

HYPERTENSION

VOLUME VI

MINERAL METABOLISM

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EDITED BY
Eric Ogden, M D
Professor of Physiology
Ohio State University
Columbus, Ohio

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INTRODUCTION

GEORGE A. PERERA, M.D.

*Department of Medicine, Columbia University College of
Physicians and Surgeons, New York City*

The subject of this year's conference makes me think of Rachel L. Carson's best seller *The Sea Around Us*. Perhaps our theme might be called *Hypertension or the Sea Within Us*.

I hope now to bring us all up to the same starting point at the water's edge so we can swim together. As you know, you and I are about sixty percent water. Into this medium the good Lord dumped a little more than one pound of salt. That pound, according to some authorities, is a mighty busy one. It races around so that well over fifty pounds cross the walls of our blood vessels in one direction or another in the course of a day. About three pounds are filtered through the glomeruli of our kidneys daily — all but a tea spoonful is reabsorbed. Plus or minus one or two teaspoons in via the diet and one out via the urine and we remain in balance with mechanisms available to handle a variety of conditions — from low salt diets to Smorga bord from the Sahara to an overdose of cascara.

The hypertension story is as follows. Based on the theory that there may be chloride retention in hypertension, Ambard and Beaujard in 1904 reported that the blood pressure fell after salt poor diet. Pfeiffer in 1911 shifted the emphasis to sodium rather than chloride. Allen and Kempner have been among the enthusiastic supporters of low sodium diets in hypertension. To day, after considerable controversy and a voluminous literature, it is accepted generally that rigid sodium restriction will often lower the blood pressure and that this is achieved directly on the peripheral resistance through the modification of a non neurogenic component. Most of us would agree that some patients have fewer symptoms, congestive failure is helped and retinopathy is improved. We debate about the heart size after salt restriction, feeling that only the failing heart gets smaller. We are troubled about the limitations and restrictions imposed on the patient, not only because of the unpleasant features and the unavailability of such diets but also because they do not seem to help the kidneys very much. In fact, if we restrict the salt too much in the presence of renal damage, the kidneys may become too much salt with resultant symptoms and further impairment of renal function. The

benefits of the low salt diets on blood pressure are less evident in patients with the accelerated form of hypertension

Let us briefly summarize a few of the results which have been reported on the experimental side. In many forms of experimental hypertension the addition of sodium chloride seems to make the hypertension worse and the pathological changes more advanced. We are under the impression that the hypertensive patient tolerates a low sodium diet somewhat better than a normotensive subject if there is no renal damage present and that other differences in response are present such as a somewhat greater sodium diuresis when hypertensive individuals are treated with thiocyanates. There are reports of an increase in sodium in the vascular musculature of hypertensive animal, of increases in total exchangeable sodium and of an abnormal distribution of tissue electrolytes in hypertensive subject. Desoxycorticosterone requires at least some dietary salt for its pressor action. Finally several groups have reported that there is an augmentation and perhaps an increased rate of excretion of a sodium load when given to hypertensive subjects in comparison to control studies in normotensive individuals.

There are also some puzzles. For example low sodium diets reduce the blood pressure but also stimulate the elaboration of aldosterone. Why no rise in blood pressure? Desoxycorticosterone in the presence of sodium elevates the blood pressure and lowers the total amount of potassium in the body, but there are several reports that a low potassium diet may lower the blood pressure. The rauwolfia alkaloids lower the blood pressure yet on occasion cause sodium retention. Why no elevation of blood pressure in these cases?

Before closing I should like to mention a few of the reasons for caution in the way we conduct our studies. Many reports in the literature dealing with sodium restriction or load fail to consider the antecedent diet of the patient. For example it takes on the average at least four days after a change in diet to achieve electrolyte balance, therefore an adequate baseline is essential. Furthermore there are big differences in patients who have a little renal damage as compared to those with no renal damage. One must be certain that renal responses do not reflect damaged kidneys rather than disturbed metabolism.

The weight of evidence today favors an association between sodium and the blood pressure. There are many reports now that lend support to the idea that there is a disturbance in sodium metabolism in hypertension. What is cause and what is effect remains to be seen, whether sodium is related to a fundamental mechanism is still in doubt. I feel sure that some of the speakers in this symposium will bring us much closer to the truth about the sea within us and perhaps in this way we will be a little less at sea.

SODIUM AND HYPERTENSION

SYMON RODBARD, M D , Ph D

*From the University of Buffalo Chronic Disease Research Institute,
Buffalo, New York*

A RELATION between the blood pressure level and the amount of salt ingested has long been suggested by the hypotensive effects of low salt diets in some cases of hypertension (1) and in pre eclampsia (2) as well as by the clinical value of a high salt intake in the control of the hypotension of adrenal insufficiency (3). A high salt intake can produce rises in blood pressure in a variety of experimental animals. Similar mechanisms may be operative in the production of essential hypertension in man.

A stimulus to the following epidemiologic study was the apparently high incidence of hypertension among Negroes. The impression that this race was particularly subject to hypertension had already been suggested by several statistical studies from the South (4,6) from prison populations (7) and from the tropics (8,9). Etiologic factors such as diseases of the kidney, the adrenal gland or the nervous system have not clarified the mechanisms of hypertension in these cases. Environmental factors such as previous history and occupation usually provide no significant clues. Recently a survey of the hypertension produced in animals by a high salt diet impelled us to re-examine the possible relation between salt intake and blood pressure level.

A further stimulus to this study came from the report of Dahl and Love (10) who asked employees of the Brookhaven National Laboratory whether they salted their food before tasting, after tasting or rarely. Their results showed that patients with blood pressures above 140/90 had a greater tendency to salt their food before tasting while hypertension was infrequent in individuals who rarely salted their food.

Salt Ingestion in Man

In this cooperative study with Dr. Milton Terris of the Department of Public Health and with Dr. Franklin Zeplovitz a questionnaire was designed to obtain information on the salt ingestion habits of patients in the associated teaching hospitals of the University of Buffalo School of Medicine. The study was broadened to include Whites as well as Negroes and a total of 210 patients was studied.

The medical records of hospitalized hypertensive patients were examined by a medical student for comparison a normotensive on the same ward.

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who was matched as far as possible for age ex height weight race and occupation was also selected These data along with the diagnosis the duration of the stay in the hospital and blood pressures on admission while in the hospital and at the time of the questionnaire were placed on a special form The names of the matched pairs without other identifying data were then given to a second student who used a second questionnaire to obtain information on previous habits of diet salt and water intake

Analysis of the data obtained showed that the following factors did not correlate with the blood pressure previous residence in the South amount of salt used in cooking whether the patient salted his beer or watermelon the volume of fluid taken and the degree of nocturia Blood pressures of the patients correlated poorly with the cause of death of parents although more than twice as many hypertensives as normotensives reported a stroke in their parents

Out of the 240 record obtained many were eliminated because of acute alcoholism (which usually gave rise to transiently elevated blood pressure levels on admission) a stay in the hospital of more than one month primary renal disease and previous treatment of hypertension as well as for unmatched case The remainder of the data could be matched satisfactorily for 126 patient The records were then divided into four categories according to the diastolic pressure at the time of the interview below 80 mm Hg in the 80's in the 90's and above 100 mm Hg Three sets of correlations then appeared

Only marginal support for the specific findings of Dahl and Love (10) appeared in the answers to questions concerning the salting of food prior to tasting Thus twenty five percent of the patients with diastolic pressure below 80 mm Hg salted their food before tasting thirty percent in the group with pressures in the 80's forty five percent with pressures in the 90's and forty percent in patients with diastolic pressures of 100 mm Hg or more (Fig 1) Our data therefore suggest that the simple salting of food at the table prior to tasting is not a sufficiently satisfactory sign of the presence of a raised blood pressure

A better correlation was found between the blood pressure level and the response to a question concerning the amount of salt used at the table (Fig 2) Thus twenty percent of the group with pressures below ninety stated that they used either *little* or *no* salt at the table while seventy percent of the patients with pressures of ninety mm Hg or more stated they used *some* or *much* salt at the table

It is immediately apparent that these qualitative terms are seriously limited since what may seem to be *much* for one patient might be *little* for another Nevertheless it was of interest that so many hypertensives seemed to think that they used considerable salt at the table while normotensives generally had a contrary impression

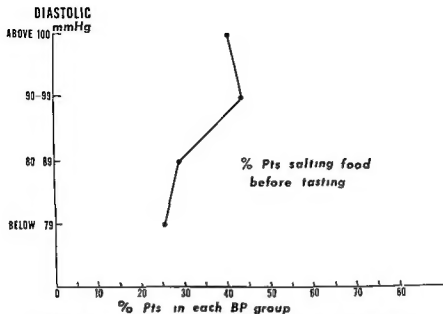


FIGURE 1 Percentage of approximately thirty patients in each of four diastolic blood pressure levels who reported that they usually salted their food before tasting

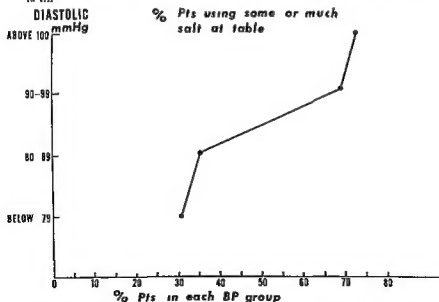


FIGURE 2 Percentage of approximately thirty patients in each of four diastolic blood pressure levels who reported that they used "some or much" salt at the table

Support for the thesis of a higher salt intake in hypertension was found in an analysis of questions concerning the intake of highly salted foods. A significant correlation was shown between the blood pressure level and the number of highly salted foods which each patient reported he ate regularly (Fig 3). A list of fifty highly salted foods was read to each patient and he

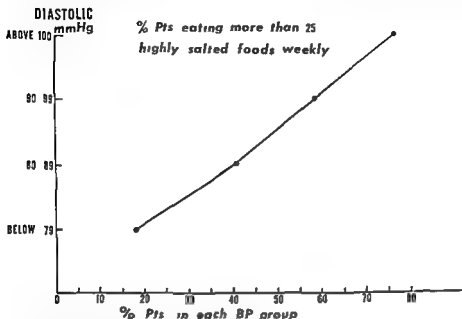


FIGURE 3 Percentage of approximately thirty patients in each of four diastolic blood pressure levels who reported that they ate more than twenty five highly salted foods at weekly intervals

was asked if he took each of these daily weekly monthly or rarely. The foods included salt or smoked fish herring cod clams crab meat flounder oyster fresh or canned salmon tuna and sardines among the meats listed were corned chipped or dried beef canned chicken smoked meats ham salt pork bologna salami liver sausages and frankfurters vegetables included sauerkraut canned corn a paragus mushrooms or tomato juice olives beans chili canned soups salad dressings and mayonnaise salted snacks included french fried or chipped potatoes pretzels salted soda crackers cheese nuts and dairy products including buttermilk salted butter or margarine.

Only twenty percent of the patients with blood pressures less than eighty mm Hg ate twenty five or more of the salted foods at approximately weekly intervals. forty percent of the patients with diastolic pressures in the 80's and fifty five percent of those with pressures in the 90's reported more than

twenty five such foods being taken while seventy five percent of the patients with pressures of 100 mm Hg or more reported this higher intake of salted foods

The data presented above suggests that hypertensive patients may have a greater than normal appetite for salty foods. A possible relation between salt intake and hypertension has recently been emphasized by Mercer (11) who reports that hypertension is so common in the Bahamas that almost everyone on these islands has a relative with the high blood, or has had a stroke or has died of hypertension. In some of these islands the drinking water is said to contain a high concentration of sodium chloride. A clinical impression is that half of the West Indians over age of forty actually have systolic hypertension by commonly accepted criteria. More than twenty percent of the males and thirty percent of the females in the third decade of life had diastolic pressures over 100. If ninety mm Hg were accepted as a criterion for diastolic hypertension two thirds of the islanders over forty would be in this classification.

A remarkable finding in the Bahamas is the high salt intake on some of the islands (11). As a baseline we may consider that the water supply in Nassau and some of the outer islands is said to contain three grams of sodium chloride per liter. In Eleuthera one of the smaller islands it is five grams per liter. If some of these natives consumed two liters of water a day they would be getting ten grams of sodium in their daily water ration alone. The Bahamians are reported to drink a great deal of water because of a constant thirst possibly induced by the hot climate as well as by a high salt intake. Further, a common item of the diet is salt pork which contains about eight grams of salt per pound.

While the relation of salt intake to hypertension is only now under intensive clinical investigation, a considerable literature on such a relation in animals has appeared in the last decade.

Salt induced Hypertension

Hypertonic salt solutions as drinking water have been demonstrated to raise blood pressure in various experimental animals. Some years ago we showed that the addition of table salt to the drinking water of the chick produced a rise in blood pressure within a few days (12). Thus 0.9 percent sodium chloride in the drinking water produced a pressure rise (optical recording) from an average of 135/125 mm Hg to an average of 155/135 mm Hg in two weeks. When the concentration of salt was increased to 1.2 percent the blood pressure increased further to 180/150 mm Hg. Within a week after normal tap water was provided the pressure fell sharply to the control level. When the animals were again placed on drinking water containing 1.2 percent salt the blood pressure rose again falling toward normal at a somewhat slower rate when the animals were once again permitted to drink tap water. The ratio of wet heart weight to body weight

the animal might properly be considered to be hypertensive compared with its own basal level. It is probable that similar problems of differentiation of normotensives with pressures in the upper range of their distribution from hypertensives in the lower range of their distribution are also

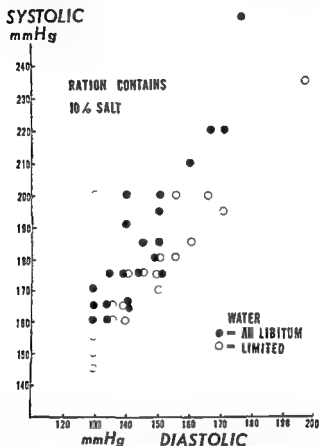


FIGURE 5 A plot of systolic vs diastolic arterial pressures in chicks at fifteen weeks of age. All animals had salt added to their mash. The solid dots represent values for chicks taking tap water ad libitum. The open circles represent values for animals receiving limited drinking water.

present in man. This would suggest that the measurement of the blood pressure alone may not be sufficient to determine the presence of a hypertensive process in a given individual.

The reduced pulse pressure of the animals on the salt diet may be related to changes in aortic tone or to a reduction in stroke output. The mechanical

have not yet been analyzed in our laboratory. The change in pressure is probably not associated with change in body fluid compartment. While a transient edema appeared shortly after the onset of a high salt intake, the weight fell in short term experiments at the end of the first week on salt and it was assumed that dehydration had probably taken place. This suggested that one of the contributing mechanisms may be the relative amounts of salt ingested compared to the water available for its excretion.

Water Intake Experiments

To test the role of water intake in salt fed animals, experiments were carried out in sixty chicks given mash to which table salt was added. In the second week of life, one percent sodium chloride was mixed with the mash; this was increased to three percent during the period three to six weeks, to five percent during the sixth week, to six percent during the seventh week, and to ten percent during the last eight weeks of the experiment.

Unlimited drinking water. Half the animals were allowed free tap water ad libitum. The feed intake per kilogram of body weight was approximately equal to that of animals on a normal mash diet without salt. These animals gained weight at a normal rate and showed no signs of toxicity. Twenty-four of the thirty animals survived to the end of the study. The blood pressures in these animals averaged 180/140 with a mean of 160 mm Hg (Fig. 5) and a heart rate of 330 beats per minute.

Analysis of the data showed that some of the animals had diastolic pressures below 130 mm Hg or distinctly within the normal range. Nine of the twenty-two chicks studied had diastolic values of 150 mm Hg or higher.

Limited drinking water. Another group of thirty chicks was given the same salted diet except that these animals were provided with only ten percent of the water taken by the first group. These animals showed toxicity and a large number of them died during the course of the experiment. The animals grew poorly, weighing only half their control. The heart rate of some of them was as slow as 250 beats per minute, but the slowed rate was unrelated to changes in pressure or in pulse pressure. At the end of the experiment, the blood pressures in this limited water group were essentially similar to the comparable group which had access to unlimited drinking water (Fig. 5).

Comparison of the results obtained with the preceding two groups shows that the development of toxicity as indicated by poor growth can result from a high salt intake. However, the availability of an adequate supply of drinking water reduces this manifestation of toxicity. By contrast, the hypertensive effects of a high salt intake seem to persist whether or not such toxicity is present. Furthermore, the hypertension induced by a high salt intake appears unaffected by the availability or restriction of fresh drinking water.

Animals taking salt in the drinking water took more salt and had generally higher pressures than did those taking salt mixed with the mash.

This may suggest that the hypertensive process is a function of the total quantity of sodium ingested. The animals taking the most salt also had larger adrenal glands per kilogram of body weight (Table 1). In man with essential or renal hypertension the adrenals are also reported to increase about twenty five percent in weight (13).

TABLE 1

EFFECT OF SALT ON BODY AND ADRENAL WEIGHTS IN CHICKS

	Number of animals	Average Weight kg	Adrenal Wt Body Wt $\times 10^4$	Salt added g/kg/ day
Water	39	1.7	9	0
Saline	13	0.9	14	9
Water ad lib	21	1.7	9	0
10% Salt in ration				
Limited Water	18	0.9	10	5

(See text for details of experiment)

Self Selection Experiment

Excess salt intake disturbs water balance and polydipsia and polyuria develop. Disturbances of the electrolyte pattern brought about by salt or desoxycorticosterone administration show that these changes depended on renal function. We have examined the role of the kidney in the mechanism of polydipsia and salt hunger (14). Rats were placed in Richter self selection cages (15) each with four graduated tubes containing either tap water or solutions of five percent glucose, 0.9 percent sodium chloride or 0.9 percent potassium chloride. The control animals preferentially took a daily average of eighty ml glucose solution and 15 ml of saline. The administration of desoxycorticosterone caused the animals to increase their saline intake to eighty ml of saline in addition to the usual glucose intake. On the first day after total nephrectomy the animals sharply reduced the saline intake to eleven ml although an average of thirty two ml of glucose solution was taken. A small amount (ten ml) of glucose solution was taken on the second day but saline was avoided. No fluid was taken on the third and fourth day after nephrectomy.

These results indicate that the increased sodium appetite induced by desoxycorticosterone is dependent on a continuing diuresis. It may be considered that the administration of DCA raises the ability of the cells of the

body to hold sodium and in this way causes a relative salt deficiency or hunger. The taking of sodium by mouth then causes considerable pillage which must be replaced. When the loss is stopped as after bilateral nephrectomy sodium appetite ceases. The role of these sodium exchange mechanisms in the development of hypertension remains to be determined.

DISCUSSION

A number of workers hold that arterial hypertension is secondary to a disturbance in the salt water balance in the body. Eichelberger (16) has shown that the sodium chloride content of skeletal muscle increases in renal hypertensive dogs while the potassium decreases and the extracellular water tends to increase. Green and Sapirstein (17) have noted that in hypertensive rats in which only a portion of one kidney remains intact the total body sodium increases as much as twenty five percent. Since the plasma sodium remains at normal level and the extracellular space is not markedly expanded some of the retained sodium probably enters the intracellular compartment. Braun Menendez (18) holds that an increase and maldistribution of sodium and water occurs in the three types of hypertension induced by disturbing the renal blood flow by removing both kidneys or by administering desoxycorticosterone.

Hollander and Judson (19) have shown that hypertensive patients have an increased ability to excrete sodium perhaps associated with an increase in intracellular sodium. They also suggest that the distribution of sodium rather than its total in the body might be related etiologically to the raised blood pressure. Muirhead *et al* (20) have reported that the administration of pressor drugs produces a rapid measurable fall in the plasma sodium with a concomitant rise in potassium; they believe these changes reflect the entrance of sodium into the cellular compartment as potassium leaves the cell. These effects are reversed at the end of the pressor infusion. Similar ionic changes in the plasma have been observed by the Friedmans (21).

Tobian and Binion (22) have reported that water and sodium accumulate in muscle, brain and in the blood vessel wall of hypertensive animals and they have suggested that the increased peripheral resistance may result from edema of the vessel wall. Such edema could act to reduce the lumen of the arterioles. From physical considerations even a small reduction in the radius of a blood vessel would markedly reduce the blood flow through it (Poiseuille) unless a higher pressure were provided.

The blood pressure will fall if sufficient sodium is lost from the body as occurs in rigid dietary sodium restriction in man. For many years a similar effect could not be produced in the dog since the sodium conserving function of this animal is so efficient that sodium loss is minimal even under conditions of rigid restriction (23). The sodium blood pressure relation is

even in this species however since intensive peritoneal lavage can reduce the plasma sodium from about 145 to 115 meq per liter with a reduction of the blood pressure to normal in hypertensive dogs. Normotensive dogs subjected to the same procedure have no fall in pressure (24)

Sodium restriction also reduces the blood pressure of hypertensive rat and increases their survival time (25). Somehow the animals seem to appreciate this physiological situation since they will decrease their sodium intake when a choice of drinking solutions is permitted. This low salt preference of hypertensive rats is maintained even after adrenalectomy during administration of desoxycorticosterone or during a forced increased fluid intake (26). On the basis of more complex experiments using the parabiotic rat Ledingham has shown that the hypertension which develops in a nephrectomized parabiont is followed by a return of the blood pressure to normal upon removal of the adrenals of the hypertensive animal. Ledingham (27) thus feels that the raised blood pressure is due to an adrenal pressor material normally eliminated or neutralized by the kidney. In previous studies we have shown that the pressor principle of Goldblatt hypertension is eliminated by a similar mechanism that is by the metabolic activity of normal kidney tissue (28).

A factor which probably contributes to the difficulty in determining a quantitative relation between sodium intake and the blood pressure level is the complexity of sodium-potassium balance. Thus a high sodium intake can lead to a period of arterial hypertension but this may be followed by the development of severe hypokalemia, generalized weakness and a fall in blood pressure to normal or even subnormal levels (29-31). The reactivity of the arterioles appears to be involved since the pressor responses to epinephrine, norepinephrine, renin and angiotonin are diminished (32). The mechanism appears to depend on the hypokalemia since administration of potassium salts to such animals causes a return of vascular reactivity to pressor drugs within an hour or so (32). In the absence of the adrenal gland potassium repletion or retention does not result in a rise in blood pressure. The administration of cortisone or ACTH will restore the reactivity and tend to raise the pressure (33). Similar effects occur in man (31). For example, orthostatic hypotension occurred in a patient who was subject to chronic potassium loss; potassium replacement improved the ability to regulate the blood pressure (34).

These hypotensive and atonic responses are related to the excessive renal potassium waste induced by a high salt intake. The sodium conserving function of the kidney is so efficient that this ion tends to be reabsorbed from the glomerular filtrate in the renal tubule; however, a potassium ion must be excreted by the tubular cells in order to accomplish some of this sodium reabsorption (35-36).

The physiological actions of sodium and potassium balance have long been studied in the isolated heart. More recently attention has been called to the ubiquitous redox pump which normally pumps sodium out of the cells while maintaining a high potassium concentration within the protoplasm (37). This action depends on the presence in adequate amounts of potassium in the extracellular fluid. For example, when the concentration of potassium in fluid surrounding frog skin is diminished, the normally high intracellular potassium is diminished while the intracellular sodium which is normally low increases (38). Conway (39) has recently shown that the sodium pump mechanism in yeast cells is more effective when potassium is present in the extracellular solution. DCA appears to weaken the ability of the cell to eliminate sodium from the protoplasm (39).

It is evident that desoxycorticosterone and certain other steroids modify sodium exchange. DCA given in large doses to dogs produces hypertension associated with disturbances in salt water balance, and this may persist for weeks after cessation of the compound (40). This hypertension is potentiated by a simultaneous administration of sodium salts (41,44). DCA produces an early retention of sodium and water followed by an increased renal loss of these materials. Subsequently a sodium appetite and hypertension develop. The disturbed sodium balance induced by DCA is evident in tissues other than the kidney, since the sweat glands (45) and the terminal ileum (46) also show a reduced sodium excretion. Long term DCA administration will ultimately result in a depletion of body potassium with the development of a anemia and a tendency to a fall in blood pressure similar to that produced by excessive salt intake. The physiological significance of DCA has long been in question. However, aldosterone has essentially similar physiological effect. It is of special interest therefore that arterial hypertension is reported to be associated with a state of mild chronic hyperaldosteronism as indicated by urinary excretion studies (47). Other substances may also produce blood pressure changes. Thus Selye has suggested that somatotrophic hormone increases the sensitivity of the rat to salt or to DCA with the induction of hypertension (48) and that other steroids such as methylandrostenediol can raise the blood pressure although this latter hypertension can be prevented by adrenalectomy (49).

When the mechanism of essential hypertension is finally clarified, salt and water regulation will probably play a significant role in its pathogenesis. The kidney, as the ultimate organ involved in electrolyte balance, would appear to be a key structure in determining the blood pressure change. The adrenal cortical effects on ionic balance and neurohypophyseal effects on water exchange probably contribute less directly.

SUMMARY

A questionnaire survey of salt intake habit of 126 matched hospitalized patients revealed that hypertensives were more likely to use some or much salt at the table while normotensives generally reported little or none salt usage. The hypertensives also reported they ate regularly (weekly) a larger number of highly salted foods (e.g. potato chips french fries salt pork ham fish etc.) than the number of these foods reported taken by the normotensives.

In experiments on chicks addition of 12 percent table salt to the drinking water or 10 percent salt in the mash resulted in a distinct rise in blood pressure in most of the animals. Animals on a high salt limited water intake tended to be stunted in growth and to have a high mortality rate. The groups taking the greatest quantity of salt had the highest blood pressures. The animals also showed larger adrenals per unit of body weight.

Some mechanisms involved in salt water balance and in blood pressure regulation are discussed.

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DISCUSSION

DR GEORGE A PERERA I have several questions I am troubled about the West Indies because on some of the islands the incidence of glomerulonephritis is high I am troubled that in New York the greater tendency of Negroes to develop hypertensive disease is limited to malignant hypertension does an excess of salt affect only one form of hypertension? When we have corrected for age we have been unable to find any difference in dietary sodium intake or sodium excretion in the urine in hypertensive versus normotensive subjects Dr Podbard did you take age into consideration? I suspect as we get older our dietary habits change

DR IRVINE H PAGE The assessment of the amount of salt people take is in some ways easier and in some more difficult than the amount of fat they eat I have tried the interrogation method with many patients and am altogether unconvinced that many of their answers are reliable True there are people who eat extreme amounts or have no taste for it at all and they know it I am concerned with the run of the mine hypertensive patient who has no strong feelings one way or the other

When I was working with Dr Van Slyke at the Rockefeller Institute he insisted that a daily or triweekly urinary chloride was the only way to get

an idea of salt intake even when the diet was believed to be rigidly controlled. This I learned to believe after we found a patient getting a large amount of salt from her tooth paste. Thus I hesitate to accept surveys purporting to determine salt intake. Until salt is actually measured I doubt if an epidemiological survey would be meaningful.

As you know Dr. Corcoran will head an expedition to St. Kitt's Island to study the incidence of vascular disease and its relation to the diet especially as it concerns salt intake. We know of the high incidence of strokes in Japanese fishing villages when salt is used as a food preservative in fantastically large amounts.

It is too easy to convince yourself of the validity of your own preconceived notions with an epidemiological survey. For instance a physician in Cleveland is convinced he has shown a direct relationship between hypertension and eating pepper and highly seasoned foods. This summer he published a note showing hypertension could be so produced in rats. Now he is more convinced than ever. You will also recall the supposed relationship to stale coffee. I would therefore plead for much more careful and penetrating epidemiological studies before a stand is taken which then the investigator feels impelled to defend.

DR. SIDNEY FRIEDMAN: I too like Dr. Perera am puzzled and troubled by a number of things. With Dr. Page I think the association of salt intake with the presence or absence of hypertension is at the moment a matter of association only. We find that if high salt diets are given to rats for sufficient periods of time (three to five months) the hypertension tends to disappear. It is a long jump and a hazardous one from the amount of salt taken in to exactly how the salt is being handled. I think the sodium handling mechanism is of fundamental importance and directly determines the state of tone of the smooth muscle cell. Therefore salt intake may be essentially determined by the salt output and that saved for the body. It seems rather tricky to try to deduce from measuring one of the parameters exactly what the relationship of the salt intake to the blood pressure level is.

Regarding adrenal size I have an anatomical bias. I feel it is difficult to decide on the basis of size whether or not an organ is hyperfunctioning. It may be impossible to decide whether a measurement of increase in size should be based on absolute size of that organ related to the animal's age or computed back to the animal's weight. The method chosen may lead to entirely different results the interpretation of which is determined by personal bias.

DR. GEORGE R. MENEELY: We studied 3,000 human beings in one group and another smaller group. Among the first there was absolutely no correlation between the amount of salt they said they ate and their blood pressures. We did sodium excretion for 24 hour periods on a few of these young draftees and found no correlation with what they said they ate.

The other group came from an industrial plant. Industry is becoming highly interested in this question since it is well known that the most valuable employee is the one with years of service and hypertension causes a relatively high loss rate for such employees. Some industries which have men working in a hot environment requiring the use of salt tablets are quite concerned about the salt question. In this industrial population we did find a correlation between the stated salt intake and the observed blood pressure. This group was middle aged, similar to that observed by Dahl, and all were healthy enough to work. Some other group mentioned here were also elected in that they were patients. I believe this election of special groups is biasing the data on possible relations between human salt intake and blood pressure.

DR HENRY A. SCHROEDER: The question of course is whether you get hypertension by eating salt or you eat more salt because you have hypertension. One of the best places to study this matter is where the salt diet is higher than it is here. The measured intake of the average Japanese is about ten grams of sodium chloride a day. Sodium intake is said to be much higher (up to thirty grams per day) in certain Japanese fishing villages and rural areas. At a meeting of the Japanese medical society last Spring I asked about twenty-five people if they had measured urinary output of sodium or chloride in hypertensive and normal people to find out how much sodium they did eat and nobody had. The Japanese had a habit of feeding soldiers extra salt in Manchuria in cold weather because studies showed that this practice raised the metabolic rate. The Japanese have more hypertension in some age groups, particularly in women over forty, than we do statistically and about as much as we have in other age groups.

About two years ago Dr. Homer Smith said there was one thing we knew about the hypertensive kidney — and much of this comes from Dr. Floobler's laboratory — that it is a salt-losing kidney. Now, if it is a salt-losing kidney and if, as we believe, the sea within us is constant and must remain a constant or we will get sick like Dr. Rodbard's dogs with low serum sodium levels, then if we lose salt we have to eat more salt. This is a question that must be studied more extensively.

DR ARTHUR M. FISHER: The percentage of patients with essential hypertension in the hospital in which I work and in my private practice who develop malignant hypertension has decreased steadily over the last twenty years. This experience is contrary to that in some municipal hospitals, particularly those that care for a large number of Negro patients. I now find it difficult to find patients with papilledema in the malignant phase of essential hypertension to demonstrate for didactic purposes. The only explanation I can offer is this: the private patient, and also the type of ward patient we have, do not eat much salt. Doctors and new papers have taught them salt is bad for them. While not on a low sodium diet, certainly not

on any approach to a 200 mg figure they consume far less salt than before. The decrease in the proportion of patient with essential hypertension who enter the malignant phase long antedated the widespread use of anti-hypertensive drugs but has been accelerated since.

As regards heredity my experience differs with that of Dr Rodbard perhaps because histories are more easily obtainable. In my material the enormous importance of the genetic factor in the causation of essential hypertension is clearly discernible.

DR JOHN H MOYER I would like to refer back to basic mechanism. About two years ago we studied the effects of saline infusions over a prolonged period of time in lightly anesthetized dogs. Our mortality rate was extremely high climbing to eighty percent after an infusion of twelve hours or more. When we used five percent glucose it was probably less than ten percent which raises a question which I pose here. In postulating that the effect of salt in hypertension is a direct one on the blood vessels why is the central nervous system always overlooked? Sodium retention may actually increase sympathomimetic activity and hypothalamic imbalance. In the experiments I just mentioned I feel these dogs died a central nervous system death. We observed some rise in blood pressure followed by vascular collapse not associated with pulmonary edema.

Secondly I want to outline a simple experiment for Dr Page if he plans to attend the forthcoming Bahamas medical conference. He and his colleagues should have their blood pressures taken every day for two weeks before departure. At the conference they should drink tap water and record blood pressures for two weeks while drinking this water which has such a high sodium content. When I was there last year I developed moderately severe edema of the ankles. Out of interest I recorded the blood pressure. I do not believe I have ever had a systolic blood pressure of over 120 before in my life but it was 135 mm Hg and remained so for about ten days after I left Nassau and returned to the States.

DR G M C MASCOV I would like to expand the remarks concerning the relationship of hypertension and the handling of salt regarding the susceptibility of various animal species to salt hypertension or to deoxycorticosterone hypertension which is a kind of salt hypertension. The most susceptible are the chick and rat which respond to salt by a severe and rapidly progressive type of hypertension. The dog is relatively refractory to salt hypertension. With large doses of deoxycorticosterone or of some of the highly active synthetic steroids the most that can be obtained is a rise of 20 to 50 mm Hg even if the animals have been adrenalectomized. They never show malignant hypertension. In the rabbit salt and deoxycorticosterone cause hypotension instead of hypertension. These are examples how that handling of salt is more important than salt intake.

DR. SIMON ROBBARD Many more problems have been raised than can be answered in the time available. Dr. Perera mentioned a high incidence of glomerulonephritis in the West Indies. I have no personal data on this but Drs. Moer, Hoobler and associates are investigating this.

The validity of questionnaires, their value in the study of an epidemiological problem and the association of specific sets of data and a given disease are always subject to careful evaluation. Correlations in a given survey may have only an accidental relation with the disease. We must face this risk in any research study of any nature. The questions we asked were prepared only after extensive consultation with experienced epidemiologists. Pairing of patients served to reduce chance associations. The correlations proved nothing concerning the relationship between salt intake and the occurrence of hypertension but they do point clearly to the need for more definitive studies on the salt hypertension question.

Our data showed no hereditary predisposition to hypertension. While the questionnaire has limitations it is more adequate than the drawing of conclusions on the basis of individual cases. In any event the relation of heredity and hypertension is far from clear and this includes analysis of clinical data in the literature.

Possible errors due to faulty memory of the patient as to what he eats are difficult to evaluate. It is hard enough to get valid information when the patient is on the metabolic ward of a research hospital. Our data can have meaning even if they represent only an ingestion fantasy or wish or guilt on the part of the patient.

It appears that many people living on the smaller islands do take large amounts of salt. Dr. Schroeder's comments are quite instructive. In this regard it is of some value to reconsider our judgments concerning normal blood pressure levels of a given cultural group. Perhaps our criteria of normal pressures belong only to our own part of the world.

Dr. Mason raises the question of species variability which becomes quite evident when we remember that even a low diastolic pressure in the chick is a severe hypertension for most mammals including man. Malignant hypertension is quite easy to induce in the dog but we have never seen it in the chick.

In answer to Dr. Sidney Friedman the weight of the adrenal gland was definitely increased in our salt-fed animals especially when compared with body weight. This appears to be a more satisfactory basis of comparison than calculating the size of the actual gland against the size of a presumed normal animal. Whether the hypertrophy is associated with hyperactivity is not known.

The remainder of our discussions in this conference will I hope provide definitive answers for some of the questions which have been raised.

SODIUM AND WATER RATIOS IN THE PATHOGENESIS OF HYPERTENSION

LEO A. SAPIRSSTEIN

*Department of Physiology, The Ohio State University,
Columbus, Ohio*

THAT there is a disturbance in the metabolism of sodium and water in human and experimental hypertension has been suggested repeatedly. Unfortunately the nature of the disturbance is not so clear as one might wish. The hypertensive subject is said to show an increased salt appetite (1) but the renal hypertensive rat shows salt aversion (2) (3). Intracellular sodium has been reported increased in hypertensive animals (4) and men (5) other studies indicate it is decreased in experimental hypertension (6). Some work suggests that sodium excretion is depressed in experimental renal hypertension (7) other investigations imply that the hypertensive animal or patient is actually a salt loser (8) (9) (10).

In an attempt to reconcile some of the observations I will show that a preponderance of the evidence indicates that in hypertensive rats there is an imbalance between sodium intake and sodium output which predispose to ward sodium retention. I will also show that this imbalance cannot be described properly unless the sodium balance is related to the balance of water.

Obviously in a chronic condition there cannot be a continuing imbalance between the intake and output of sodium. A previous period of imbalance may leave its imprint on the body's sodium content and concentration but this may be concealed in a short term metabolic study.

For the most part a history of positive sodium balance cannot be obtained practically. Instead we must rely on evidence which suggests that increased sodium intake has exceeded the excretory capacity or that damage to the excretory mechanism has reduced the excretory capacity below normal. Only direct determination of body sodium can demonstrate a preexisting positive balance of sodium if indeed such exists.

Much data is available indicating that excessive ingestion of sodium presumably above the level which can be effectively excreted induces hypertension.

McQuarrie (11) first reported the development of hypertension after giving massive doses of sodium chloride to diabetic children. Later Lenel, Rodbard and Katz (12) described the rapid development of hypertension in the chicken receiving isotonic or hypertonic saline in its drinking water. Sapiro, Brandt and Drury (13) made rats hypertensive by substituting hypertonic (2 percent) saline for drinking water. The results were confirmed by

Mason and Corcoran (14) and by Mucio *et al* (15) Meneely (16) demonstrated the occurrence of hypertension in the rat exposed to a high salt diet

The clear relationship demonstrated by Dahl and Love between the subjective evaluation of salt consumption in man and the incidence of hypertension suggests that the adult human subject may be similarly affected by excessive salt intake The epidemiologic studies of Moyer (17) among the natives of the Bahamas whose well water contains large quantities of sodium chloride and who do play an extraordinarily high incidence of hypertensive disease are also impressive However there is also a very high proportion of hypertensive disease among the Virgin Islanders (18) who are said to use rain water rather than well water for drinking and cooking

There is ample evidence to suggest that the sodium content of the body is increased in the animal made hypertensive by renal manipulation or salt loading This phenomenon was first noted by Eichelberger (19) in the muscles of renal hypertensive dogs Laramore and Grollman (20) later described an increase in the sodium concentration of most organs in renal hypertensive rats Similar findings were reported by Greene and Sapirstein in the renal hypertensive rat (4) Mucio *et al* (15) reported very substantial increases in the salt content of the skeletal muscles heart and liver of rats made hypertensive by salt feeding Tobian (21) and Tobian and Binion (22) (23) found increased concentrations of sodium in the aortas of hypertensive human subjects and renal hypertensive rats

When sufficiently large groups of hypertensive animals or patients are studied a tendency for the plasma sodium concentration to be elevated is almost universally found (Kyllin and Elmquist 24 Holley *et al* 25 and Fregly *et al* 26) Disappointingly the changes are small The biological significance of such findings must remain in doubt particularly when one notes the failure of rats exposed to kidney encapsulation at an older age to show elevation in serum sodium (26)

Are reported increases in organ sodium content of biological significance? Grollman and his associates (27) (28) have shown a clear increase in the mannitol and radio sulfate spaces of hypertensive dogs and men the same has been noted by Ross (5) Since only slight elevation of extracellular fluid volume is required to increase greatly the sodium content of tissues and organs the possibility that these increases are due to a minimal edema cannot be ruled out with certainty It seems improbable that expansion of the extracellular space could have any but a casual relationship to the hypertensive process particularly when we remember that pontaneous edema and isotonic sodium chloride loading (29) are without important effects on the arterial pressure

Ross studies (5) suggest that the excess exchangeable sodium of hypertensive men may be intracellular but the possibility that the excess is all equated in bone though considered was not ruled out The work of

Ledingham (6) indicating that intracellular sodium may actually be depressed in the hypertensive heart and skeletal muscle is also disturbing. In a small series Moore *et al* (30) failed to demonstrate that exchangeable sodium of the body was elevated in hypertensives.

The chance that the hypertensive subject may have a decreased ability to excrete sodium receives very little experimental support. Except for one study in renal hypertensive dogs (7) the opposite appears true. On the other hand, as will be shown below, an excretory deficiency toward sodium can be uncovered in the hypertensive rat or human subject but only when water retention is simultaneously considered.

Braun-Menendez' description of the water and chloride excretion of the fasting hypertensive rat is especially illuminating (31). Chloride excretion of the hypertensive rat did not differ appreciably from that of the normotensive; the hypertensives however showed considerable polyuria. In effect though the hypertensive urine contained about the same amount of chloride as the normotensive it was being excreted at a much lower concentration.

Some elementary considerations may be helpful at this point. If one considers that the cells of the body are bathed in an environment of 300 mOsmol/l, it is clearly of much less concern to the cells whether the volume of the environment changes than whether the composition of the environment is altered. It would appear unlikely *a priori* that 300 mOsmol/l volume changes in the extracellular fluid would produce significant physiological effect. When changes in osmolarity occur however, one might reasonably anticipate that the cells would react. Thus a loss of sodium in hyperosmolar solution resulting in hypoosmolar contraction of body fluids might logically have the same physiological effect as gain of water without sodium resulting in hypoosmolar expansion. Similarly sodium gains in excess of water producing hyperosmolar expansion of the body fluids might be expected to have the same cellular effects as water losses in excess of sodium producing hyperosmolar contraction of body fluid.

Although in a qualitative sense these propositions are self-evident it is sometimes difficult from a cursory examination of the sodium and water balances of the organism to determine the status of the fluids remaining in the body. For example it is not immediately obvious whether an individual losing 100 meq of sodium chloride in a liter of urine has suffered a great distortion in body fluids as one who has lost 150 sodium meq in two liters of urine.

A simple formula fundamentally similar to that of West & Rapoport (32) to describe the water economy of the kidney in osmotic loading relates the behavior of sodium to water in its effect on body fluid. The sodium saved for the body through renal formation of urine is the product of the urine volume and the difference between the plasma sodium and urinary sodium

concentrations. The sodium described is sodium in excess of water—in effect free sodium. The sign of free sodium may be positive, signifying that the kidney has conserved sodium in excess of water, or negative, meaning the body has lost more sodium than water through the kidney.

In the example cited above, assuming a plasma concentration of 150 meq Na per liter, the free sodium change represented by the loss of a liter of urine containing 100 meq/l is +50 meq of sodium. The individual losing 150 meq Na in two liters of urine has a positive free sodium balance of 150 meq. Although sodium losses of the second individual exceed those of the first, free sodium saved to the body is much greater in the second. In effect he is in negative sodium balance compared to the first on the basis of mass of sodium lost, but when the simultaneous water losses are considered, he is in a positive sodium balance with respect to water when compared with the first individual.

When the studies on urinary excretion of salt and water are analyzed in this light, a rather striking consistency emerges. For example, Green (8) has shown that hypertensive patients are salt losers. But the salt losses under basal conditions or loading with isotonic saline are associated with disproportionately large losses of water in the hypertensive group when the free sodium calculation is made, the hypertensive group is seen to be in positive free sodium balance, though they are at the same time in negative balance of sodium.

The data of Weller, Cottier and Hoobler (33) are quite similar to those of Green, and may be amenable to the same interpretation.

TABLE I
WATER AND SODIUM LOSSES BY HYPERTENSIVE
AND NORMAL RATS

(12 Hour Metabolic Period)

No Load

10 Hypertensives			10 Normals		
U ₂₄ V	V	F ₂₄	U ₂₄ V	V	F ₂₄
meq	ml	meq	meq	ml	meq
2.87	27	1.20	1.72	7	-0.65

Difference HT — N = 1.85 meq F₂₄

Applying the same principles to chloride, the findings of Birchall *et al.* (9) reveal an identical pattern. Although chloride excretion is three times greater in the hypertensive than in the normotensive subject, the free chloride status shows the normals in negative balance for this ion (with respect to water) while the hypertensives are in positive balance.

Ledingham (6) indicating that intracellular sodium may actually be depressed in the hypertensive heart and skeletal muscle is also disturbing. In a small series Moore *et al* (30) failed to demonstrate that exchangeable sodium of the body was elevated in hypertensives.

The chance that the hypertensive subject may have a decreased ability to excrete sodium receives very little experimental support. Except for one study in renal hypertensive dogs (7) the opposite appears true. On the other hand, as will be shown below, an excretory deficiency toward sodium can be uncovered in the hypertensive rat or human subject but only when water retention is simultaneously considered.

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Some elementary considerations may be helpful at this point. If one considers that the cells of the body are bathed in an environment of iso osmotic salt, it is clearly of much less concern to these cells whether the volume of the environment changes than whether the composition of the environment is altered. It would appear unlikely *a priori* that iso osmolar volume changes in the extracellular fluid would produce significant physiological effects. When changes in osmolarity occur however one might reasonably anticipate that the cells would react. Thus a loss of sodium in hyperosmolar solution resulting in hypo osmolar contraction of body fluids might logically have the same physiological effect as gain of water without sodium resulting in hypo osmolar expansion. Similarly sodium gains in excess of water producing hyperosmolar expansion of the body fluids might be expected to have the same cellular effects as water losses in excess of sodium producing hyperosmolar contraction of body fluids.

Although in a qualitative sense these propositions are self evident it is sometimes difficult from a cursory examination of the sodium and water balances of the organism to determine the status of the fluids remaining in the body. For example it is not immediately obvious whether an individual losing 100 meq of sodium chloride in a liter of urine has suffered as great a distortion in body fluids as one who has lost 150 sodium meq in two liters of urine.

A simple formula fundamentally similar to that of Weitz & Rapoport (32) to describe the water economy of the kidney in osmotic loading relates the behavior of sodium to water in its effect on body fluids. The sodium saved for the body through renal formation of urine is the product of the urine volume and the difference between the plasma sodium and urinary sodium.

TABLE IV
WATER AND SODIUM LOSSES BY HYPERTENSIVE
AND NORMAL RATS LOADED WITH 1.5% NaCl
(6 hours)

17 Hypertensives			17 Normotensives		
U, V	V	F _v	L, V	V	F _v
meq	ml	meq	meq	ml	meq
41.4	154	-18.3	57.5	108	-21.2
Difference HT - N = 2.9 meq F _v					

plausible picture of the hypertensive disturbance evolves. One may speculate that the basic disorder in hypertension is that the body fluids are always on the verge of hyperosmolarity. This teetering on the brink may result from hyperosmolar loading due to an excessive intake or production of osmotically active substances; alternatively such loading may result during normal intake and production of solutes because of diminished water intake. Even when the water intake and production and ingestion of solutes are normal the kidney's damaged ability to save water for the body may induce hyperosmolarity of the body fluids.

Ancillary evidence in support of this hypothesis comes from the findings of Ellis and Grollman (30) that hypertensive dogs and men show increased urinary levels of antidiuretic hormone. The lowered water content and elevated cation content of the organs of salt hypertensive rats (15) and the higher cation and nitrogen content of rats with renal hypertension (4) are consistent with this view.

Against this theory is the fact that hypertension can persist in human subjects in the presence of hyponatremia. Peripheral resistance may not be increased in such subjects; however, since the cardiac output is not known. The higher than normal water content of hypertensive organs (20, 23) appears to argue against the hypothesis of hyperosmolarity. But when it is recalled that slight expansion of the extracellular fluid, which has a much higher water concentration than intracellular fluid, will produce such changes without change in osmolarity, it becomes questionable if water content of tissues gives useful information regarding the hydration of cells.

One wonders whether in hypertension treatment should not be directed to the possibility that the presumed defect in the regulation of osmolarity may be remedied by increasing water intake rather than by decreasing the intake of salt, which is after all only one of the osmotic loads placed on the kidney. To this writer's knowledge no studies have been made on this point.

SUMMARY AND CONCLUSIONS

There is much evidence to indicate that hypertension is associated with abnormal accumulations of sodium in the body. At the same time it appears that both human hypertensives and renal hypertensive animals actually excrete more sodium in any given experimental circumstance than normotensives.

The apparent paradox can be resolved by relating the sodium economy of the body to its water economy. When this is done it is almost consistently seen that hypertensives though they lose sodium in excess of normotensives also lose water in excess of normotensives. These abnormalities in excretion are such that relatively more water is lost than sodium so that the hypertensive subject or animal does tend to accumulate sodium at least with respect to water.

It is suggested that hypertension may follow hyperosmolarity of the body fluids whether this is induced by loading with hypertonic salt restriction of water or a renal inability to conserve water in relation to osmotically active solutes.

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DISCUSSION

DR SIMON ROBBARD In the work I described this morning it was shown that chickens feeding on ten percent salt and restricted as to water intake did not develop as much hypertension as did the control animals on an unlimited water intake I wonder how these observations can be reconciled with Dr Sapirstein's views

DR HENRY A SCHROEDER This all inclusive term hypertension

does not represent a uniform group. All kinds of renal disease may be present and of any one kind all stages of degeneration of one or both kidneys. The ability of the kidneys to handle electrolytes may therefore differ widely from patient to patient. This may account for some of your discrepancies. Metabolic balance studies of patients on constant intakes of water and salt do not result in dehydration even when water is relatively restricted for long period. The group of hypertensive animals may be more uniform than hypertensive patients but the kidney's ability to handle water and salt and make ammonia probably varies according to the degree of disease or disorder present. Also there are probably several etiologies of hypertension furthering lack of uniformity. This theory is fascinating in regard to experimental animals but it may not make sense in human beings. If the hypertensive is really a relative sodium saver although he is actually a sodium waster he must eat more salt because he has to have extra salt even though he is saving it relative to his body fluid concentration.

DR SIBLEY HOOBLER: In our water and sodium excretion studies in which the same individual has been studied at different blood pressure levels or in which hypertension of various etiology has been examined the blood pressure level has correlated reasonably well with sodium and water excretion*. Also Dr Dustan's work shows in general that when there is an obstructive renal arterial lesion with unilateral reduction in renal arterial pressure sodium and water output on this side are usually reduced. Our own belief is that sodium and water excretion can be correlated with the local pressure within the renal artery. We know of no clinical or laboratory investigation that contradicts this generalization originally suggested by Selkurt and Shipley in their work on isolated kidneys and we believe increased sodium and water excretion in hypertension is a function of pressure within the renal artery rather than some general metabolic disturbance although what arterial pressure does to kidney cells it may also do to other cells of the body.

Since Dr Moser is not here and he has been quoted several times I shall try to speak for him. What you have heard about drinking rain water in the Virgin Islands does not apply to the Bahaman natives. Dr Moser went down there and observed that in the inhabitants of the Bahamas urine volume and water and salt intake were very high. He also found sodium output in the urine very high. They were not drinking rain water.

DR LEO A. SAPISTEIN: As I recall the group on restricted water weighed less than half as much as the group allowed water ad lib. It seems probable to me these animals had so great a reduction in plasma volume and cardiac output that an increased peripheral resistance may have existed and was

Cott, P. T., Weller, J. M., and Hoobler, E. W.

Effect of an intravenous sodium chloride load on renal hemodynamics and electrolyte excretion in essential hypertension.

Univ. Michigan Conf. on Hypertension, Circulation vol 17 April, 1958 (In press)

not displayed as hypertension simply because the animals were unable to maintain a normal cardiac output

Dr Schroeder states that hypertensive patients in long term metabolic studies stay in water balance. I do not think there is any real doubt that this has to be the case. Obviously any patient with a chronic disease must remain in balance for any inorganic substance during the course of his disease. But patients can differ with respect to internal level of a substance required to achieve balance. I believe in any long term balance study on a hypertensive with respect to water and sodium his internal level of water and sodium is quickly adjusted to the level required to maintain balance subsequently.

It is true as Dr Schroeder states that hypertensive patients include a varied group. That is precisely why it is so remarkable that water wasting in excess of sodium is so regularly reported in the literature. I know of only this one exception which occurs under the unphysiological condition of osmotic loading. In such loading the free sodium calculation sometimes shows the hypertensive to be gaining less free sodium than the normal. However in terms of water economy which is ordinarily the reverse side of free sodium at least when sodium is the principal osmotic load on the kidney the hypertensive still demonstrates his tendency to lose water in excess of osmotically active solute. It is a monotonously regular finding not only in hypertensive animals but also in hypertensive men.

Although as Dr Schroeder has reported the changes in the alkali metal in the serum are by no means impressive it is not so clear that osmolarity control is preserved as well as the sodium and potassium levels. For this freezing point determinations would have to be made. I do not know if anyone has done this.

Dr Hoobler notes that water and sodium excretion are increased as a function of the pressure in the renal artery. I think the issue here is this: Are the two increased in proportion to each other? If water excretion is increased more than sodium excretion one can anticipate secondary changes in the organism which could conceivably result in the perpetuation of the hypertension. Thus a kidney in a temporarily hypertensive animal might by excreting water in excess of salt duplicate the conditions in an animal ingesting salt in excess of water (which leads to hypertension). This is a perfect setup for a vicious cycle in which a temporary hypertension is converted into a permanent one.

I meant to emphasize that Moer had done his work in the Bahama Curiously in the Virgin Islands where rain water is drunk the incidence of hypertension is also very high. In a way the two stories supplement each other. In the Bahamas Moer notes the natives drink much salt water and suffer from constant thirst. In the Virgin the natives drink a little bit of fresh water and are perpetually short of it. The common denominator of the two seems to be not excess of salt but shortage of water free of salt.

EXPLORATION OF RENAL EXCRETORY MECHANISMS WITH RADIOACTIVE SODIUM AND POTASSIUM

FRANCIS P. CHINARD, M.D.

*Departments of Medicine and Physiological Chemistry,
The Johns Hopkins School of Medicine and the Medical Division,
Baltimore City Hospitals Baltimore Md*

During the past twenty years a spate of publications has appeared on renal functions in health in disease and in frequently drastic experimental situations. What may be called the grosser aspects are firmly delineated. We know what to expect clinically from deficiencies or excesses of certain endocrine products from deficiencies or excesses of various components of the diet from certain types of structural damage and even from changes of posture. Changes in the handling of water and of sodium by hypertensive individual and animals are under intensive scrutiny. There is for example the recent striking application of experimental studies as a diagnostic tool in determining the management of patients with hypertension and one type of unilateral renal disease (1, 2).

In substance there is available a large body of empirical and practical knowledge. Interpretations of these data and of studies of species other than man have led to rather definite classical concepts of the complex mechanisms involved in the renal handling of sodium water and other substances. As new experimental facts emerge the validity of these concepts is questioned. Procrustean techniques may be required if the concepts are not to be modified.

What follows is a progress report on continuing experimental studies in dogs of certain features of the renal handling of sodium potassium and certain other substances. Because the techniques and procedures used have not received wide application these are described below and some of the results obtained in studies with substances other than sodium and potassium are outlined briefly.*

EXPERIMENTAL PROCEDURE

Anesthetized mongrel dogs are used as subjects. Infusions are given via catheter in a jugular vein. When required a midline abdominal incision is

*The studies have been carried out in collaboration with Dr Theodore Enn, Dr W. Rowland Taylor and Mr. Mary F. Nolan and have been generously supported by the Life Insurance Medical Research Fund, the Markle Foundation, the Veterans Administration, the United States Public Health Service, the United States Atomic Energy Commission, the Eli Lilly and Company and Mr. & Mrs. Sharp and Dohme. The assistance of Miss C. L. Le, Mrs. B. Green, Miss W. H. and Mr. A. McCoy and Mr. J. Armand in the course of these studies is gratefully acknowledged. For a preliminary report and certain preliminary details see references (3) to (8). The results shown in Figures 2, 4 and 8 are from unpublished studies.

made and a catheter is inserted into the left renal via the inferior vena cava and tied in place. Blood is drawn through the catheter by means of a pump. The bladder is exposed, opened and a catheter is tied in place in each ureter. A left flank incision is made and by retroperitoneal approach the aorta and left renal artery are exposed. Injection of test solutions is made through a bent needle inserted into the aorta and turned up into the renal artery.

The injection solution contains the blue dye T1824 which is assumed not to leave the circulation to a significant extent on passage through the kidney, a glomerular substance such as inulin or creatinine which is neither excreted nor reabsorbed by the tubules, and the appropriate test substances. The injection is made in less than two seconds. Following the injection, some thirty samples of blood are obtained from the renal vein catheter over a period of about one minute. Thirty or more samples of urine are obtained from each ureteral catheter separately over a total period of five to twenty minutes.

RESULTS

Glomerular substances

Before applying the procedures to other substances it was necessary to show that on passage down the tubules diffusion effects were minimal and that little or no separation of glomerular substances occurred. Pairs of glomerular substances were tested and results of the type shown in Fig. 1a for inulin and creatinine were obtained. The ordinates indicate the fractional excretion in each sample of urine for each substance.

Sample number after injection is given along the abscissae. The effects of recirculation are evident in that there is significant excretion of inulin and creatinine from the right kidney. Accordingly, correction for this is made by subtraction of the amounts excreted in each sample by the right kidney from the amounts excreted in corresponding sample by the left kidney. The resultant values are then plotted to give the excretion curves or patterns shown in Fig. 1b. There is little difference between the two curves. Similar results were obtained in other experiments (3). There is no evidence of substantial separation of the glomerular substances on passage down the tubules.

Virtual volumes

It was soon noted that the positions of these excretion patterns varied with the rate of urine flow. More specifically, the appearance times, the modal (peak) transit times, and the mean transit times (9) all were dependent on the rate of urine flow. The variation of appearance time with urine flow had already been well documented (10). Further, our procedure was not sufficiently refined (the duration of each urine collection period was too long) to permit obtaining data of the requisite accuracy. Accordingly, attention was focused on the mean transit times. The product of the mean transit time and the urine flow has the dimensions of a volume. The relationship of these volumes is calculated to the rate of urine flow is

shown in Fig 2 (see (4) for earlier data) The volumes are roughly twice the urine flow

Similar calculations are made in studies of the circulation by the dye dilution method A vascular volume between the point of injection and the point of sampling = calculated from the mean circulation time and the car

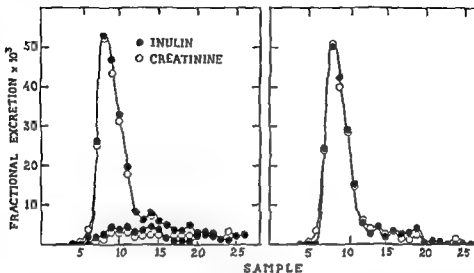


Fig 1a Excretion patterns of creatinine (circles) and of inulin (dots) following injection of a solution containing both substances into the left renal artery The upper curve is for the fractional excretion from the left kidney the lower curves are for the fractional excretions from the right kidney Each sample represents a 12 second collection period

Fig 1b Excretion patterns of creatinine (circles) and of inulin (dots) after correction for recirculation Data from experiment shown in Fig 1a Data from this experiment are from ref (3) and are reproduced by permission of the editors of *The American Journal of Physiology*

diac output or flow These calculated volumes obtained from data with glomerular substances might then be similarly considered to represent the volume of urine between the glomeruli (the transit time from renal artery to the glomeruli is quite small) and the end of the ureters (correction has been made for the catheter volumes) No correction has been attempted for the volumes in the ureters (probably quite small compared to the urine flow because of the rapid peristalsis) and for the volumes in the renal pelvis Nonetheless this implied relationship between urine flow and volume of urine in the kidney may have its counterpart in histological observations The columnar epithelium is reportedly flat and the lumen large in tubules from kidneys excreting urine at a high rate of flow the epithelium is raised and the lumen is inconspicuous in tubules from kidneys excreting urine at

a low rate of flow* Possibly the functional variations observed at very high rates of urine flow as in osmotic diuresis may be related to these presumed morphological variations

Apart from these considerations the fact that excretion of the glomerular substances is accomplished not in a very sharp peak but is distributed over

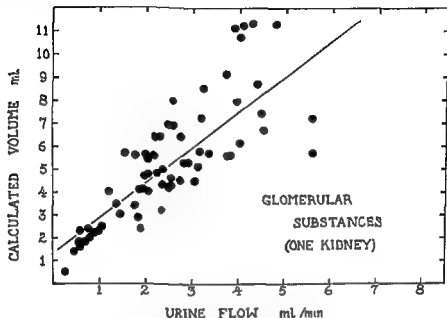


Fig 2 Relationship of calculated volumes for glomerular substances to rate of urine flow The straight line is regression line V_c on the rate of urine flow (least squares method) Values given are for one kidney

several minutes and that the injection takes place in less than two second points to a dispersion of nephron functions and/or structures As shown later quantitation of this dispersion is possible Also in conventional clearance studies under steady state conditions it might be more appropriate to take as correction for delay time either the modal or the mean transit time rather than the appearance time

Urea

The clearance of urea is substantially lower at all urine flows than the clearance of glomerular substances In the dog and in man there is no evidence pointing to active transport of urea in either direction across the tubule cells That the clearance of urea is lower is apparently the result of simple back diffusion of urea from tubular lumen to peritubular fluid In the type of experiment described above the recovery of urea in the urine should be

*An illustration of these changes is given in "A Textbook of Histology" by A A Maximow and J W Bloom 2nd Edition W B Saunders Co Philadelphia 1937 p 479

le than that of a simultaneously injected glomerular substance. In addition there should be some skewing of the urea curve relative to that for a glomerular substance: some of the urea that had diffused from tubular lumen to tubule cell would be expected to diffuse back to the lumen as the front of C¹⁴ labelled urea proceeded distally down the tubule. In Fig 3 are shown the results of an experiment with C¹⁴ labelled urea and creatinine. The urea curve is lower than that for creatinine and it is skewed so that the excretion of urea is delayed relative to the excretion of creatinine. The calcu-

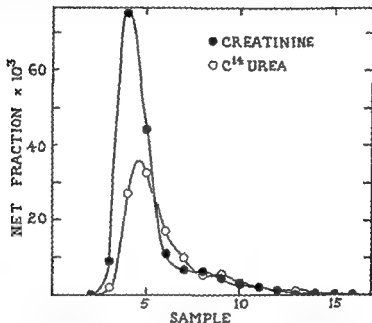


Fig 3 Excretion pattern of creatinine (dots) and of C¹⁴ labelled urea. Data from this experiment are from ref (51) and are reproduced by permission of the editors of *The American Journal of Physiology*.

lated volume available to urea is greater than the calculated volume available for creatinine. In spite of the permeability of cells to urea there is no evidence to permit the suggestion that urea has jumped the gap between peritubular fluid and tubular lumen via the back door: the excretion of urea is delayed relative to the excretion of creatinine. Such results are compatible with the conventional concept of the renal handling of urea.

Reabsorbed substances

Substances which are reabsorbed actively by the tubule cells may be considered to be secreted from tubular lumen to peritubular fluid — a direction opposite to their concentration gradient. If reabsorption is

complete none of the substance appears in the urine this is what happens with glucose. However if an appropriate load of glucose is delivered to the tubules reabsorption is incomplete and glucosuria occurs. Under such conditions the excretion curve of C 14 labelled glucose should be lower than but symmetrical to that of simultaneously injected glomerular substance. Fig 4 shows the results of an experiment with C 14 labelled glucose and ordinary creatinine under conditions of glucose loading. The results are

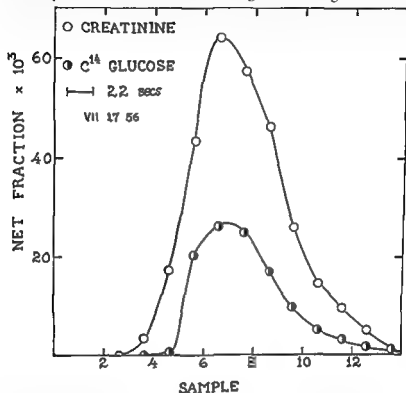


Fig 4 Excretion patterns of creatinine (dots) and of C 14 labelled glucose in presence of glucosuria

essentially as predicted. There is however an initial delay in glucose excretion this delay remains to be explained.

Phlorizin blocks the tubular reabsorption of glucose. Following its administration the excretion curves of C 14 labelled glucose and of creatinine should be identical. The results of such experiments are as predicted though the initial delay in the glucose excretion is again noted.

Similar results have been obtained with xylose which is reabsorbed to a much lesser extent than glucose.

Renal handling of glucose

In conventional clearance studies it has been tacitly assumed that there is relatively little utilization of glucose by the kidney. Various

mechanisms have been proposed for the tubular reabsorptive process. Breakdown and re-synthesis of the six carbon chain has been suggested. In order to test the several possibilities a series of experiments was carried out with glucose, the emphasis now being placed on the patterns obtained in renal venous blood. Here the usefulness of T 1824 becomes evident. Fig. 5 shows the results of a typical experiment in which glucose-1 (labeled in the 1 position with C 14) creatinine and T 1824 were injected. The ordinates are calculated in the same manner as in the experiments in which urine was collected. The abscissal scale is different in that the collection of the thirty or more renal venous blood samples is completed in one minute or so instead of the five to twenty minutes required for the collection of the

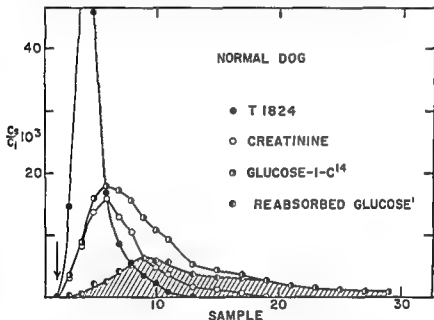


Fig. 5 Renal vein patterns. Injection of 1-C¹⁴ glucose with creatinine and T 1824. See text for details. Data are from ref. (7) and are reproduced by permission of the editors of *Science*.

same number of urine samples. The curve for the C¹⁴ labelled glucose is substantially higher than that for creatinine in the later periods. That the C¹⁴ activity was associated almost entirely with glucose was demonstrated by enzymatic methods and by radioautography. That the C¹⁴ activity in all samples had remained in the 1 position was demonstrated by a combination of stepwise chemical and enzymatic degradations of the glucose. There was no evidence of randomization of the C¹⁴ and hence no evidence of breakdown and re-synthesis of the 6 carbon chain. The recovery of creatinine rela-

tive to T 1824 averaged approximately 70 percent while the recovery of glucose averaged approximately 100 percent. It was tempting to suggest that the difference between the glucose and creatinine curves represented glucose transported by the tubules. Evidence substantiating this suggestion was provided by similar experiments carried out after phlorizin had been admin-

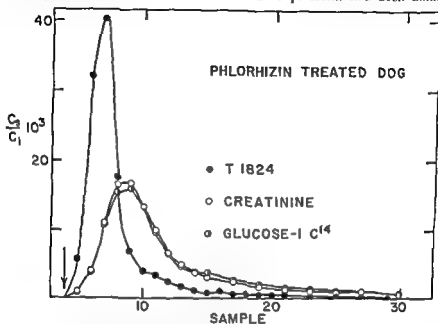


Fig. 6. Renal vein patterns of 1-C¹⁴ glucose, creatinine and T 1824 after administration of phlorizin. Data are from ref. (7) and are reproduced by permission of the editors of *Science*.

istered. Under such conditions the glucose and creatinine curves in renal venous blood should be nearly identical. Fig. 6 shows that this is the case. On the basis of these and similar experiments it was concluded that the glucose was transported with the 6 carbon chain intact and that the differences between the glucose and creatinine curves could be used to construct a recovery curve for the transported glucose. The mean transit time for this moiety of the glucose was about ten seconds greater than the mean transit time for creatinine. The transit time across the tubule cells must then be less than 10 seconds since a few seconds must be required for the glucose in glomerular fluid to travel down to the tubule cells concerned in its reabsorption.

Sources of renal vein carbon dioxide

As indicated the recoveries of glucose in renal venous blood without prior administration of phlorizin averaged about one hundred percent relative to T 1824. Because of the limitations of the recovery calculation a more

direct approach was required to determine whether significant degradation of glucose to carbon dioxide occurred during a single circulation through the kidney. To this end the renal venous blood samples were collected anaerobically and the carbon dioxide in the samples was analyzed for radioactivity. Less than 0.1 percent of the radioactivity injected as C-14 glucose was recovered as carbon dioxide. Glucose does not contribute significantly to renal vein carbon dioxide under the conditions of the experiments.

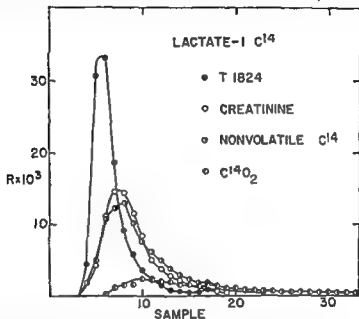


Fig 7 Renal elimination patterns of C-140 after injection of lactate-1 C-14

The elimination of glucose as a major direct source of renal carbon dioxide suggested that other potential sources should be investigated. Both lactate and pyruvate have been tried. Results obtained with C-14 labelled lactate are shown in Fig 7. A substantial fraction of the injected radioactivity is recoverable as carbon dioxide. The chemical nature of the non-volatile C-14 activity has not yet been determined. The transit time relationships permit the calculation of a mean reaction time of about four seconds for the transformation of lactate to carbon dioxide. Similar results have been obtained with pyruvate. Control experiments involving the injection of labelled bicarbonate into the renal artery have provided somewhat surprising but no unpredictable results; there is apparently substantial fixation of carbon dioxide by the kidney.

These results are preliminary. However, this technique offers the possibility of studying not only the metabolic activities of organs *in vivo* but also

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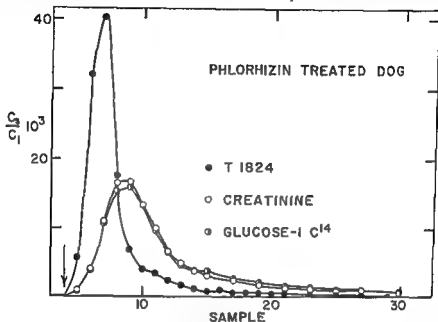


Fig. 6 Renal vein patterns of 1-C¹⁴ glucose, creatinine and T1824 after administration of phlorizin. Data are from ref. (7) and are reproduced by permission of the editors of Science.

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Sources of renal vein carbon dioxide

As indicated, the recoveries of glucose in renal venous blood without prior administration of phlorizin averaged about one hundred percent relative to T1824. Because of the limitations of the recovery calculations, a more

tration the recovery of hippurate in urine is less than that of creatinine possibly because of binding of the hippurate to the plasma proteins. The vagaries of the creatinine curve illustrate one of the difficulties encountered with this technique and result from irregular and unequal urine flows from the two kidneys. Experiments with PAH and I 131 labelled diodrast have given results which parallel closely those obtained with hippurate.

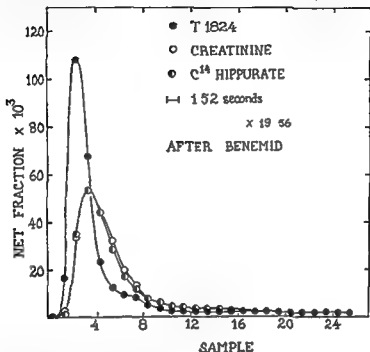


Fig 8b Renal vein patterns of C 14 labelled hippurate creatinine and T-1824 Effects of prior administration of Benemid

Relative to the velocity of urine down the tubules hippurate is brought quite rapidly to the tubule cells by way of the peritubular fluid. The delay in excretion of hippurate may therefore be considered in large part a measure of the time required for the secretory process to take place. This delay averages about seventy seconds a considerably longer time than is required for the secretion of glucose in the opposite direction. It is evidence for the transient storage during the secretory process of hippurate and its congeners in the tubule cells. Our results are consistent with those that have led to the development of the I 131 labelled diodrast renal uptake test (11).

The renal handling of potassium

Early ideas about the renal handling of potassium consisted in the simple hypothesis that urinary potassium was filtered potassium that had escaped

tubular reabsorption Occasional clinical reports indicated that the clearance of potassium could be greater than the clearance of inulin or creatinine Because the data were obtained in studies of patients with renal disease the valid

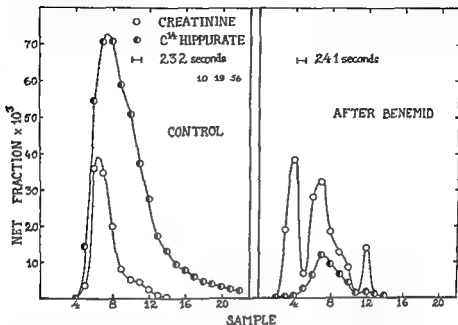


Fig 9 Excretion patterns of creatinine and C14 labelled hippurate The left panel shows the control experiment The right panel shows the effects of prior administration of Benemid

ity of the inulin clearance as a measure of the glomerular filtration rate was questioned Subsequently Mudge Foulks and Gilman (12) and Berliner and Kennedy (13) demonstrated that under occasionally drastic experimental conditions in dogs the clearance of potassium could be made to exceed substantially the concomitant clearance of creatinine This established that potassium secretion could occur Subsequent work led to the current hypothesis that under ordinary circumstances all the potassium excreted in the urine stems from distal tubular secretion and that all of the potassium crossing the glomerular barrier is reabsorbed by the tubules and returned to peritubular fluid

Further studies particularly those of Black (14) and of Morel (15) showed that there was an extraordinary uptake of radioactive potassium $K-42$ on a single passage through the kidney and that urinary excretion of this $K-42$ was related to gradual release from a pool in the kidney rather than to $K-42$ freshly arriving to the kidney from the renal artery Our own studies confirm these later findings and are consistent with the hypothesis that most of the urinary potassium stems from tubular secretion Figures 10

11 and 13 illustrate results of experiments in which both renal venous blood and urine samples were obtained Fig 10 shows that under the usual conditions of the experiments there is almost complete uptake of K-42 by the kidney and that there is gradual protracted release to renal venous blood

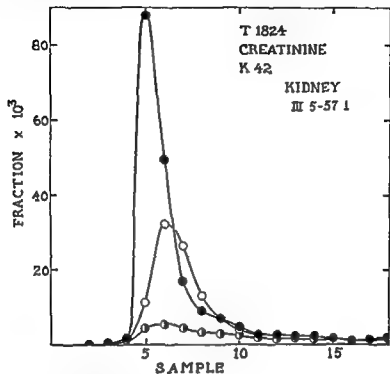


Fig 10 Renal vein patterns of T 1824 creatinine and K-42 "r" indicates duration of sampling interval

of the K-42 as demonstrated by the tailing of the curve. Under similar conditions the urine excretion curves show an unusual pattern (Fig 11). There is a peak of K-42 excretion which substantially precedes the peak of creatinine excretion. Again in the urine there is protracted tailing of the K-42 excretion. The potassium is not all accounted for in the duration of these experiments. A large fraction remains in the kidney, mainly in the cortex as shown in Fig 12 in which the relative radioactivities of different portions of the kidney are plotted. Under conditions of higher potassium clearances the recovery of K-42 in the renal vein is increased (Fig 13) as is the peak of potassium excretion in the urine (Fig 14). Finally under conditions similar to those used by Mudge and his collaborators to achieve clearances of

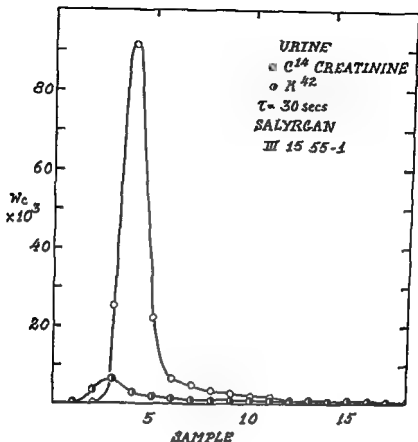


Fig 11 Excretion patterns of creatinine and K^{42} after the administration of Salyrgan

ordinary potassium greater than clearances of creatinine (12) the overall uptake by the kidney is further decreased as shown by the greater recovery in renal venous blood (Fig 15) In the urine the K^{42} peak is almost as high as the creatinine peak

As indicated these results are consistent with the hypothesis of tubular secretion of potassium The early urine peak may be considered to represent the potassium brought to the distal portions of the nephrons by way of the peritubular fluid thus accounting for the shorter appearance time and modal transit time of potassium relative to the corresponding times for creatinine The secretory process for potassium would then be fast compared to that for PAH and possibly of equal rate to that for glucose The tailing of K^{42} in

the renal venous blood and in the urine reflects gradual release from a large potassium pool probably in the more proximal portions of the nephrons*. It appears from the rough reciprocal relationship between uptake and excretion of potassium that there may be two distinct potassium pools in the kidney the capacities of which are variable and inversely related. Ordinarily the proximal pool has a high capacity and the distal pool a low capacity so that the clearance of potassium is low. When the clearance of potassium exceeds the creatinine clearance the capacity of the proximal pool is decreased and that of the distal secretory pool is increased. Under the latter conditions the possibility of some contribution to urinary potassium of potassium escaping tubular uptake cannot be excluded by these experiments.

The Renal Handling of Sodium

While the results and interpretations just presented may have some novel features by and large they dovetail in satisfactorily with other known facts and concepts about renal functions and metabolism.

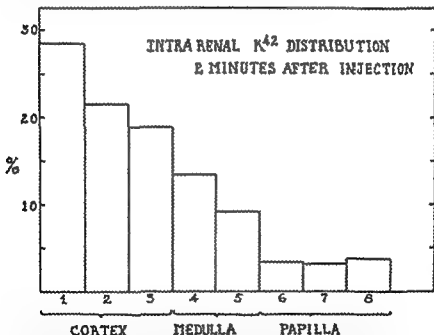


Fig. 1. Distribution of K^{42} in sections of a kidney removed and frozen in liquid nitrogen two minutes after the injection of K^{42} into the renal artery.

By a combination of radioautographic and histochemical techniques Eisen and Harris (Nature 180: 448-49, 1957) have demonstrated that the retained K^{42} two minutes after injection is indeed largely in the proximal tubule cells.

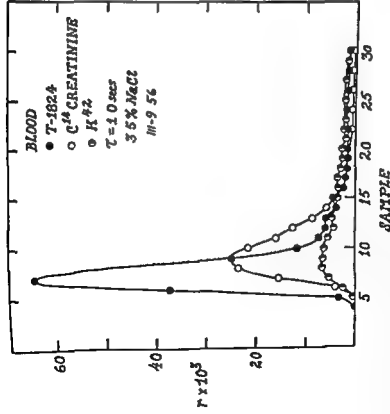


Fig. 13 above Renal vein pattern of T 1824 creatinine and K-42 after admini tra
tion of 3.5% NaCl

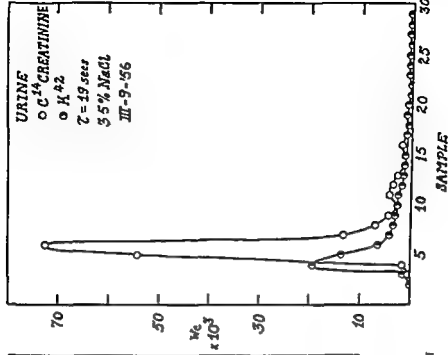


Fig. 14 right Ex retion patterns of creatinine and l K-42 after administration of
3.5% NaCl Data fr in same experiment as shown in Fig 13

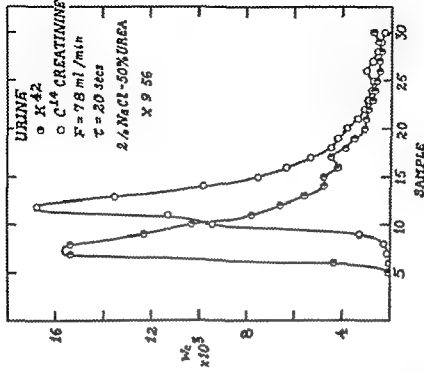
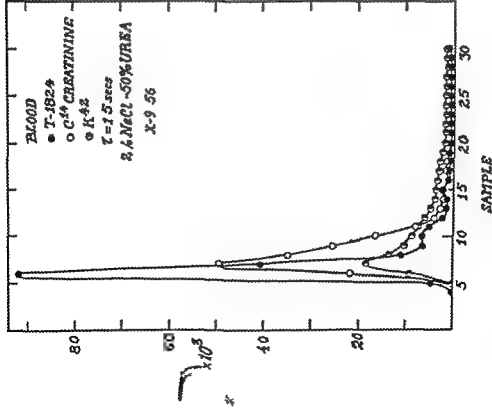


Fig 15 left: Renal vein patterns of T-1824 creatinine and K⁴² after a initial tra-

tion of 2% NaCl and 50% urea
 Fig 16 above: Excretion patterns of creatinine on 1.8.12 after a initial tra-

tion of 2% NaCl and 50% urea. Data from same experiment as shown in Fig 15

If urinary sodium is solely sodium that has escaped tubular reabsorption then one would expect to find in the urine a curve for sodium lower than but

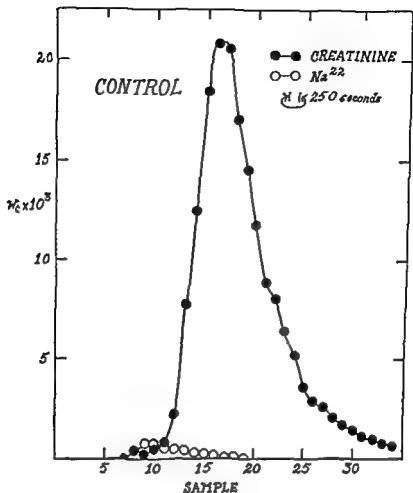


Fig 17 Excretion patterns of radioactive sodium and creatinine Control experiment

symmetrical to that for a simultaneously injected glomerular substance. Such a relationship has not been found.

Following the simultaneous injection of labelled sodium and of creatinine there is invariably found precession of sodium over creatinine (Fig 17). The appearance time, the modal transit time and the mean transit time of sodium are always significantly less than the corresponding times for

glomerular substances. When a diuretic such as chlorothiazide (Diuril) was administered following the control experiment just mentioned the peak excretion of sodium was substantially increased and more sodium was ex

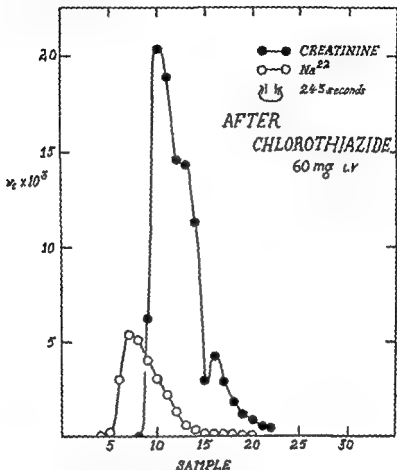


Fig 18 Same after chlorothiazide (Diuril)

creted under the creatinine curve (Fig 18). With mercurial diuretics the peak is increased but there is even more excretion under the creatinine curve. The sodium curve has however never been found to be higher than the creatinine curve except in the first few samples.

Table I summarizes some of the data obtained with radioactive sodium. To calculate the values shown in the 1st column the total of each substance excreted is determined and is assigned the value of 100. The cumulative per

TABLE I
Summary of sodium studies

Type of experiment	Number of experiments	Average percent of injected sodium excreted*	Average percent of creatinine excreted at 50 percent sodium excretion*
Without mercurial diuretic	13	16 ± 09	83 ± 83
After mercurial diuretic	8	39 ± 21	331 ± 117

*Means and standard deviations

centiles of these totals are then calculated and plotted as ordinates with sample number as abscissal values. From the curves connecting the appropriate percentile values the percent of the total eventually excreted creatinine is determined at that time or sample when 50 percent of the total eventually excreted radioactive sodium has been collected in the urine. This value permits quantitative assessment of the precession of sodium over creatinine. In all experiments this is significant since the mean transit times and the modal transit times for sodium are invariably less than the corresponding transit times for glomerular substances. There is scatter. However the precession appears to be quantitatively less when a mercurial diuretic is used. In paired experiments in which a control run was followed by a run after administration of a mercurial diuretic the precession decreased quantitatively.

Figure 19 presents the data from the chlorothiazide experiment in another manner. Here the cumulative percentile excretions are plotted as probit units along the ordinates while a logarithmic scale is used for the sample numbers along the abscissa. The marked change in urine flow after chlorothiazide was accompanied by a shift of the creatinine curve without a change of slope suggesting that little or no change occurred in the dispersion of this particular nephron function. The slope of the sodium curve was changed significantly suggesting that more than one distribution might now be involved in the excretion of the labelled sodium. This change of slope is even more marked in experiments in which mercurial diuretics were administered.

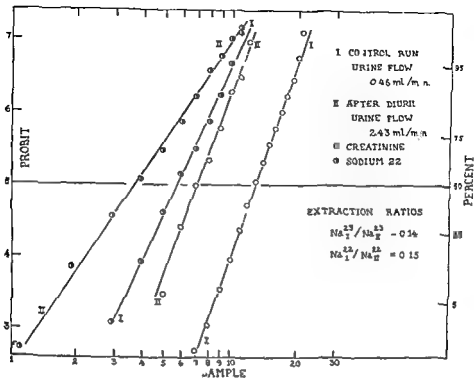


Fig 19 Probit log sample number plot of experiment shown in Figs 1 and 18
See text for details

A matter of some importance is the extraction fraction of ordinary sodium and of labelled sodium. In this and other similar experiments the extraction fractions have been approximately the same. There is no unexpected dilution of the labelled sodium.

The data can be summarized in yet another manner by calculation of the virtual volumes for sodium as was done earlier for glomerular substances. The values calculated for sodium V_N are smaller than those calculated for glomerular substances V_G . The difference $V_G - V_N$ may represent the volume of urine in the nephrons between the glomeruli and the site of delivery of the radioactive sodium into the urine. The values found in a series of experiments are shown in Fig 20. The lowest values for the differences were obtained in experiments in which mercurial diuretics were used.

Current views on the excretion of sodium can be summarized as follows. Analyses of glomerular fluid in amphibians and mammals show that the concentration of sodium in this fluid is the same as that in plasma within the

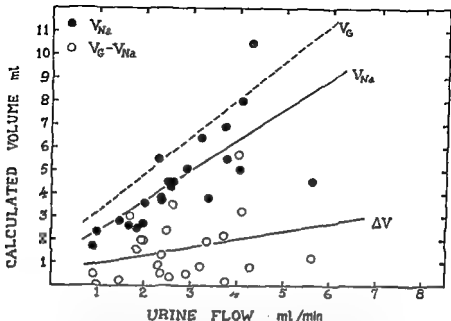


Fig 20 Relationship to urine flow of calculated volumes for sodium (V_{Na}) for creatinine (V_G) and for differences of these values (ΔV) for each experiment. The dashed line is the regression line (least squares) of V_G on the urine flow for the experiments shown here and differs slightly from that shown in Fig 3 for these and other experiments. The upper line is the regression line of V_{Na} on urine flow; the lower line is the regression line of ΔV on urine flow.

constraints of the Gibbs-Donnan equilibrium. Ordinarily the amount of sodium excreted per minute is a small fraction of the amount calculated to cross the glomerular barrier. Clearances of sodium greater than concomitant clearances of glomerular substances have not been reported. The logical deduction can be made from these facts that excreted sodium = sodium that has escaped tubular reabsorption.

The data presented above are not compatible with this hypothesis. The appearance time, the modal transit time, and the mean transit time all indicate that the excreted sodium arrives in the urine in large part via a short cut or by pass. Much of the excreted sodium must cross directly from peritubular fluid to the tubular lumen. It might be suggested that the precession of sodium (which we have also found with radioactive chloride and with ordinary thiocyanate) is simply the result of a diffusion ion-exchange mechanism and has no bearing on the renal handling of sodium. In the case of thiocyanate, for example, a thiocyanate ion in peritubular fluid would be exchanged for a chloride ion in the tubular lumen, thus permitting the thiocyanate ion to escape into the urine ahead of simultaneously injected creati-

nine which must percolate down the tubules. With this mechanism it would still be necessary 1) to consider that there was complete reabsorption of thiocyanate crossing with creatinine into glomerular urine and 2) to accept the reality of a short cut or bypass for thiocyanate. In addition there is some difficulty in visualizing a simple ion exchange mechanism operating across the structural complexities of the tubule cells. Such a mechanism would require permeability of the barrier to sodium chloride and thiocyanate and impermeability to urea, urea with a diffusion coefficient nearly as large as the diffusion coefficients of the cations does not show precession over creatinine (*vide supra*).

In brief we wish to offer the following as a tentative working hypothesis on the renal handling of sodium. Under ordinary conditions of sodium excretion in the dog proximal reabsorption is almost complete; the sodium excreted in the urine is added to the tubule urine in the distal portions of the nephrons by mechanisms quite unknown. After administration of a mercurial diuretic there is apparently some escape from reabsorption in the proximal portions of the tubules. This hypothesis is strictly applicable only to anesthetized dogs under our experimental conditions. We hope to carry out shortly similar but far less drastic studies in man.

If this hypothesis is correct a revision of the classical views on the renal handling of sodium will be in order and the possibility of tubular secretion of sodium will have to be considered.

SUMMARY

A new technique has been developed for the exploration of various renal functions. Injection of test substances is made rapidly into a renal artery of anesthetized dogs. Some thirty renal venous blood samples are obtained over a period of one minute while a like number of urine samples are obtained from each ureter separately over a period of five to twenty minutes. Plots of the fractional recoveries against time after injection provides characteristic recovery or excretion patterns for the individual test substances.

With pairs of glomerular substances such as inulin and creatinine identical excretion patterns are obtained; there is no significant separation on passage down the tubules.

The positions of the curves vary with the urine flow. From the mean transit times and the urine flows virtual volumes of distribution between the glomeruli and the end of the ureter are calculated. The volumes are approximately twice the urine flows.

The excretion curve of urea is delayed with respect to that for creatinine and the recovery of urea is less as expected from the hypothesis of back diffusion of urea.

The renal handling of glucose is examined in some detail. Glucose is transported across the renal tubule cells with the 6 carbon chain intact. It does not contribute significantly directly to renal vein carbon dioxide while

lactate and pyruvate do. In the presence of glucosuria the excretion pattern of C 14 labelled glucose is roughly symmetrical to that for glomerular substances.

The excretion patterns of PAH, hippurate and diodrast are delayed relative to the patterns of glomerular substances. Approximately seventy seconds are required for the movement of these substances across the tubule cells.

Excretion patterns of K-42 reveal that the peak excretion of K-42 precedes the peak excretion of simultaneously injected glomerular substances. There is in addition protracted excretion of the K-42 at a low rate. The recoveries of K-42 in renal venous blood are small indicating substantial uptake by the kidney tissue. With potassium clearances equal to or exceeding clearances of creatinine renal uptake is decreased but the peak excretion of K-42 is markedly increased. It is suggested that there are two distinct pools for potassium in the kidney of variable and roughly reciprocal capacities. A proximal pool is involved in the uptake while a distal pool is involved in the excretion of potassium.

Excretion patterns of radioactive sodium show a similar precession over simultaneously injected glomerular substances. Ordinarily the precession is such that about eight percent of the eventually excreted creatinine is in the urine when fifty percent of the eventually excreted sodium has been collected. The precession of sodium is decreased after mercurial diuretics.

It is suggested that ordinarily most if not all the filtered sodium is reabsorbed and that excreted sodium has been added directly to distal urine from peritubular fluid. After mercurial diuretic some of the excreted sodium may be derived from glomerular fluid by escape from tubular reabsorption.

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DISCUSSION

DR HENRY A SCHROEDER What happened to potassium after a mercurial diuretic?

DR FRANCIS P CHIVARD Diamox alone produces an increase in the peak potassium excretion. If this is followed by a mercurial such as Saltyrgan the potassium peak becomes decreased as does the fractional excretion of potassium just as the clearance of potassium increased by Diamox is decreased by subsequent administration of a mercurial diuretic.

DR LEO A SAPIRSTEIN Do you have evidence of a decrease in proximal tubular reabsorption of sodium during osmotic loading?

DR FRANCIS P CHIVARD After an osmotic load there appears to be an increase in the early part of the sodium excretion. Also there is evidence that more comes down from the glomeruli no matter what osmotic load is used. Mannitol for example causes an increase in both the peak and the later position. With sodium sulphate loading the peak is again elevated but

there is still more excretion under the creatinine curve presumably because of the presence of obligatorily excreted anions

DR THOMAS FINDLEY May I ask if you think water could be secreted also?

DR FRANCIS P CHINARD We have done a number of experiments with labeled water but the curves themselves are not very informative because of their spread. The appearance time for water is smaller than that for creatinine and about the same as that for sodium and potassium. The peak of the water curve is delayed with respect to that of creatinine. Presumably some of the water may behave as does urea entering tubule cells from the lumen and returning eventually to the lumen. For the water the curve could be broken down into three or more constituent curves. Our data do not permit any conclusion as to the possibility of water secretion.

DR MEYER FRIEDMAN Any other questions? If not I presume this is the case within us. One undoubtedly could use the inulin clearance just as easily as the creatinine?

DR FRANCIS P CHINARD A series of experiments was carried out in which pairs of glomerular substances were tested. The pairs were creatinine and inulin, inulin and ferrocyanide, and ferrocyanide and creatinine. No significant differences were detected in the curves, fractional excretions or time parameters of the paired substances.

CHRONIC SODIUM CHLORIDE TOXICITY AND THE PROTECTIVE EFFECT OF POTASSIUM CHLORIDE*

GEORGE R. MENEELY, M.D. and CON O. T. BALI

*Departments of Medicine and Preventive Medicine and Public Health,
Vanderbilt University School of Medicine, Nashville Tennessee*

A LEGACY from evolution is an exceptionally good mechanism for water and salt retention and for excess potassium excretion (1). From pre-recorded history the need for salt is indicated in the herbivores' great treks to salt licks and the carnivores filling their needs from their natural diet of the flesh of other animals (2). Legacies of history are the saline wars, slavery, decapitation and other strong measures (3-6). Legacies of the 19th century are rich and varied (7). In 1807 Davy isolated potassium and later that same year he isolated sodium also by electrolysis. By 1850 Carl Schmidt (8) was reporting determinations of sodium and potassium in the blood in his essay on cholera. He and Redtenbacher (7) are commonly credited as the first who paid scientific attention to salt in disease states but as Gamble (9) has pointed out the honor really lies with the London physician O. Shaughnessy twenty years earlier. In the ensuing hundred years the merit of salt withdrawal in edema, heart failure and hypertension has been discovered and rediscovered (10-11). Observations and experiments in the 20th century are more familiar to all of us (12-19). Allen (20) in 1922 considered low sodium diets important in hypertension and the rice diet of Kempner (21) some thirty years later is an example of the widespread application of such theories. Selye (22-23) produced nephrosclerotic like lesions in chicks fed large amounts of salt. Sapirtein (24) produced renal lesions and hypertension in rats by providing only salted drinking water. The minimal sodium requirements for many laboratory animals have been determined and the need for salt for the growth of farm animals is well proven. However despite this knowledge little is known of the actual requirements for mammals and what if any constitutes a toxic level particularly on the basis of long continued intake. Our investigations of the possible toxic effects of chronic dietary sodium chloride initially centered on the hypothesis of a threshold and the hypothesis of lag. Findings early in 1953 focused our attention on the possible relation to potassium intake accordingly life span experiments were started in which the potassium to sodium ratio in the diet was brought toward one.

*Supported in part by the Research Laboratory and Radioisotope Service, Thayer Veterinary Administration Hospital, the Life Insurance Medical Research Fund, G-56-1 and the National Institutes of Health H-1816.

Early Findings

In the initial experiment started in 1951 six groups of thirty five week old male Sprague Dawley rats housed in constant temperature humidity controlled quarters were placed on complete purified diets identical except for sodium chloride (25)

A basic ration of 25.1 percent purified Ca casein 51.8 percent sucrose 20.0 percent hydrogenated vegetable oil a complete vitamin mixture and 2.9 percent mineral mixture (26) without added sodium chloride was prepared

SODIUM SPACE

Sample	% NaCl	N	\bar{x} Na Space \pm SE
2 - 4 months			
Control	0.15	7	23.8 \pm 0.75
High salt \bar{x} edema	7.0, 8.4 & 9.8	11	26.1 \pm 0.61
High salt \bar{c} edema	7.0 & 9.8	11	57.7
8 - 10 months			
Control	0.15, 0.2 & 1.1	28	23.1 \pm 0.70
Added salt	5.6	10	24.7 \pm 0.65
High salt	7.0, 8.4 & 9.8	40	27.2 \pm 0.67

Fig. 1 Sodium space measured with Na^{24}

and found to contain 0.01 percent NaCl. Diets were derived by the addition of powdered sodium chloride intimately mixed. The control diet contained 0.15 percent NaCl. The other five groups received progressively higher proportions of sodium chloride: 2.8, 5.6, 7.0, 8.4 and 9.8 percent.

It is worth noting that the salt content of the 2.8 percent NaCl ration compares roughly on a weight for nutrient basis with the human intake of about 12.15 grams a day, a common estimate of the salt in the diet in this country (27).

The rats had free access to the diets and in later experiments 11.2, 20.1, 40 and 21.0 percent NaCl as well as demineralized water.

When first placed on high sodium chloride marked polydipsia and polyuria but only mild anorexia occurred. After three days the rats appeared to be severely dehydrated. Two weeks later the rats all looked healthy and were gaining weight regularly.

In the initial experiment average weight gains for the first twenty weeks were 353 grams control ration, 331 grams 2.8 percent NaCl, 315 grams 5.6 percent NaCl, 310 grams 7.0 percent NaCl, 295 grams 8.4 percent NaCl and 274 grams 9.8 percent NaCl (28). The earliest untoward finding (29) was during the third and fourth months when edema developed in 18 percent

of the rats eating the three highest levels of sodium chloride. Sudden weight gains of 40 to 160 grams occurred. Extracellular water measured with radio active sodium (30) rose from the control level of 24 percent to 58 percent of body weight.

The edematous animals were severely anemic and showed lipemia and hypoproteinemia. At autopsy there were obvious edema and anemia. Other wise microscopically all the tissues except the kidneys appeared normal. In relatively bloodless glomerular tufts there were foam cells containing large



Fig. 9. Early glomerular lesion (H & E). Reproduced with the permission of the Editors of the Journal of Experimental Medicine.

amounts of fat staining material. The tubules exhibited a nephrotic degeneration and contained also much fat staining material. There were lesser deposits of lipid in some of the arterioles.

Three edematous animals survived this phase rapidly lost their extra fluid and became extremely emaciated and cachectic. Again all tissues seemed essentially normal in the gross except the kidney. A renal lesion similar to that described above but more extensive was observed. Many glomerular tufts were obliterated. Tubular degeneration was extreme. No evidence of adrenal failure was found. There was widespread arteriolar disease of all the parenchymatous organs (31).

During an eight month period about fifteen percent of the test animals on high salt rations in the first and in the six succeeding experiments de-

veloped renal failure. Among those which did not there was a high incidence of elevated blood pressure. In the animals which developed renal failure massive edema occurred abruptly and sometimes was so extreme that the extracellular fluid (measured with radioactive sodium) accounted for more than one half of the total body weight. At this phase the rats were severely anemic, hypoproteinemic, azotemic, lipemic and had elevated blood pressure. As I have said, three rats in the first experiment lost their extra fluid and entered a state of cachexia. Two rats entered this terminal state without developing edema. The hearts, livers, kidneys and adrenal glands usually were hypertrophied. The kidneys showed a diffuse degenerative disease involving all parenchymal elements. The glomeruli were fused and almost bloodless due to the accumulation of sudanophilic lipid and the degeneration of basement membranes. There was severe lipid degeneration of the tubular epithelium. The arterioles underwent fatty degeneration and sclerosis (32).

Blood Pressure

Systolic blood pressure measurements were made by the cuff method of Kerston *et al* (33). At the end of the ninth month in the first experiment and as early as the second in later experiments reliable reproducible observations were obtained. At the ninth month of Experiment 1 to our immense astonishment we found an almost perfectly linear relationship between the average blood pressure (the mean for the group) and the amount of salt in the diet (34). There is quite a bit of scattering. The highest group, those eating nearly ten percent of salt, had a mean systolic blood pressure of about 155 but the levels ranged from about 210 down to something under 130. Three months later scattering is less and the mean blood pressure has gone up considerably in all groups.

In later experiments (35-38) the association of hypertension and high dietary sodium chloride was evident from the fourth month. A total of 622 male and 21 female rats have been subjected to the experimental regimen with increments of NaCl as the sole variable in the purified diet. The mean elevations of blood pressure were somewhat less in the female. Comparable hypertension was produced in seven females by feeding commercial chow with added NaCl. Females eating 5.6 and 9.8 percent sodium chloride mated with normal males and delivered apparently normal young without developing symptoms of eclampsia, although the number of pregnancies, the sizes of litters, and the survival of the young were unfavorably influenced.

In addition to the early nephrotic syndrome, increased sodium space and elevations in systolic blood pressure (39-41) there was evidence of shortened life span (42) proportional to the levels of NaCl added to the purified diets. Other unfavorable physiologic and nutritional threshold and lag effects were noticed (43). Serum cholesterol as measured by the method of Pearson *et al* (44).

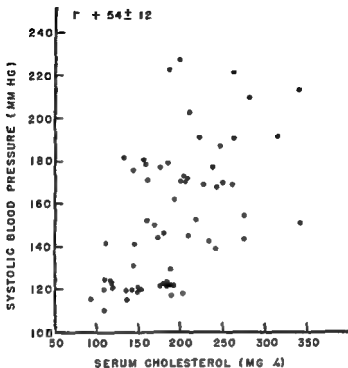


Fig 3 Elevated serum cholesterol not exhibited by normotensive rats

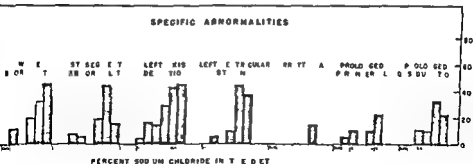
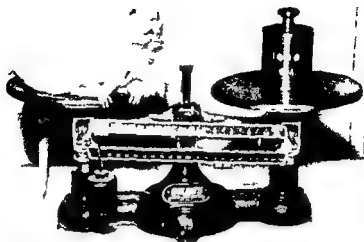


Fig 4 Distribution of electrocardiographic abnormalities at 19 months



DODSWORTH

0.15% NaCl - AT 20 MONTHS

BLOOD PRESSURE 122 - SERUM CHOLESTEROL 178

Fig 5 Obese rat on control ration normal electrocardiogram

was elevated in young as well as in middle and older aged rats. In a blind analysis of 90 electrocardiograms* after nineteen months (corresponding to late middle age) on the experimental regimen the incidence of electrocardiographic abnormalities paralleled the degree of hypertension and the concentration of NaCl intake. Rats eating 14.0 percent NaCl were dead at fifteen months; those on 21.0 percent at nine months. Some eighty percent of the group eating 9.8 percent NaCl (the highest dietary level in this analysis) exhibited abnormalities. The electrocardiographic abnormalities in these elderly rats correlated well with hypertension and cardiac hypertrophy at autopsy.

Maturity Characteristics (15)

In the nutritional effects as in the physiologic we have consideration of threshold and of lag. Early growth and development were adversely affected by the increment of NaCl. The highest salt diets, 14.0 and 21.0 per

cent resulted in a high mortality threshold early in the course of the experiment. The maximum body weight attained was related to the amount of salt in the diet (46). The mean body weight of the control group was significantly higher than the other groups ($P < 0.01$). Obesity, most pronounced in the control group, was observed in animals at all levels up to and including 5.6 percent NaCl. It was not seen among rats eating 7.0 percent or more of NaCl in the diet. One grossly obese control rat weighed over 1000 grams at twenty months. His electrocardiogram was within normal limits and his systolic blood pressure 122 mm Hg and total serum cholesterol 178 were very near the mean values of the control group. The control rats continued to gain weight for seventeen months longer though not significantly than the 2.8 percent (fifteen months) and 5.6 percent (sixteen months). In the groups consuming 7.0 percent or more NaCl the average weight gaining period was significantly shorter. The mean systolic blood pressure measured during the month in which the maximum weight was attained was significantly

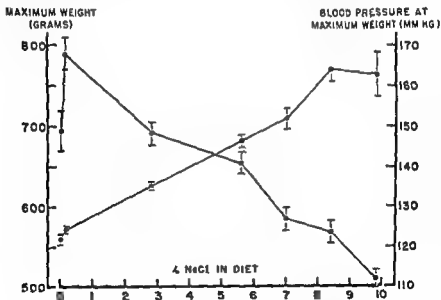


Fig. 6 Blood pressure at maximum weight.

higher ($P < 0.01$) in all groups eating added salt. The blood pressure at maximum body weight is not synonymous with the maximum blood pressure exhibited during the life span. This distinction is important in appraising the highest levels of salt feeding as the mean maximum blood pressures attained by these groups were well above the levels exhibited at maximum

MEAN AND STANDARD ERROR OF THE MEAN

LENGTH AT
DEATH (CMS)

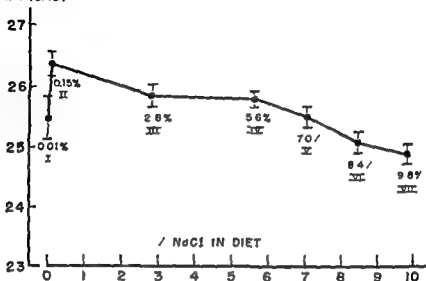


Fig 7 Average length at death — Experiment 1

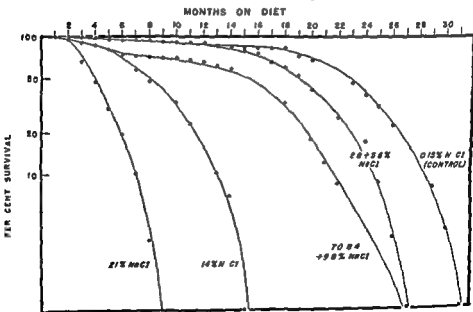


Fig 8 Survival curve

weight. The average body length at death measured from the tip of the nose to the tail base at autopsy followed the maximum weight attained pattern, i.e. the controls were significantly larger than groups eating 70 percent or more of NaCl.

Longevity (42, 43, 45, 46)

Twenty one and 140 percent NaCl resulted in high mortality early in the course of the experiment. Decreased survival in the group eating 70-98 percent NaCl was detectable from the fifth month. The other level controls 28 and 56 percent present the especially striking feature of identical survival until the fifteenth or sixteenth month of exposure to the diet approximating late maturity or early senescence. It is noteworthy that the rats eating 28 and 56 percent NaCl the levels most reasonably related to human consumption did not die at an excessive rate until after the seventeenth month. They had been mildly to moderately hypertensive from the ninth month but only this late in life does the lag effect of increased dietary salt exact its penalty. Considering these experiments on a time schedule adjusted to the human lifespan (ten days for rat equal one year for man) benign essential hypertension appears in the third or fourth decade but only in the early fifties is the sur-

MEAN AND STANDARD ERROR OF THE MEAN

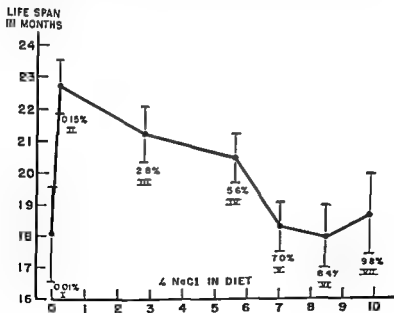


Fig 9 Average adrenal weight — Experiment I

vival rate noticeably different This is remarkably similar to the pattern the naturally occurring disease follows in the human being

Analysis of data on wet organ weights at death must take into account the variations in body weight and the variations in age of the rats at death Animals less than twelve months old at death were considered as young

MEAN AND STANDARD ERROR OF THE MEAN

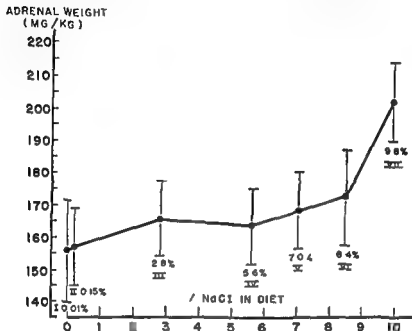


Fig 10 Average life span - Experiment I

thirteen to nineteen months as middle aged and twenty or more months as old Organ weights were expressed as weight of the organs in grams per kilogram of body weight Mean heart weight increased as the dietary salt intake increased the greatest cardiac hypertrophy being evident at the 9.8, 14.0 and 21.0 percent NaCl levels These increments were consistent with the increases in blood pressure Relative heart weights in rats dying or sacrificed in youth were similar until the NaCl intake was at the 7.0 percent level After twenty months on the experimental regimen the increased relative cardiac weight was apparent at the 2.8 percent level Renal hypertrophy followed a similar pattern The relative adrenal weight changes were less consistent The smallest relative adrenal weights were found among the 0.15 percent NaCl control animals and the 2.8 percent NaCl the greatest at intakes of 7.0, 21.0 percent NaCl In rats dying during the first year increased

adrenal size was related to amount of dietary salt. A converse relationship was evidenced in those dying after twenty months.

The arteriolosclerotic lesions in the fifteen percent of the rats eating high levels of salt which developed the early nephrotic syndrome have been discussed. Among the remainder life span was shortened hypertension developed there was a disturbance of lipid metabolism renal and heart failure occurred all in proportion to the amount of NaCl in the diet. The spectrum of hypertensive cardiovascular renal disease seen in the human was reproduced ranging from a clinical course resembling that of mild benign essential hypertension with minimal shortening of life span to rapidly progressive and lethal malignant hypertension.

Arteriolar lesions (29, 31, 32, 39, 40, 41) occurred in incidence, extent and degree proportional to the increase in dietary sodium chloride and to the severity of the clinical course. In the more advanced disease the renal arterioles were uniformly involved. Stainable lipid formed vacuoles in smooth

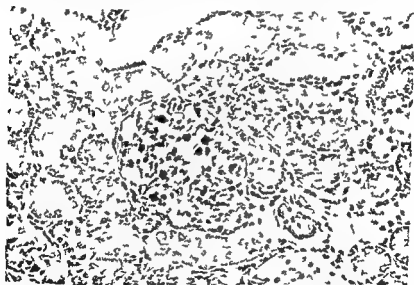


Fig. 11. Glomerular lesion, tubular lesions and arteriolar necrosis. Reproduced with permission of the Editors of the *Journal of Experimental Medicine*.

muscle cells, some of which were necrotic. In many arterioles the elastic lamina was greatly swollen, frayed and intensely eosinophilic. The lumina were narrowed or even occluded. Visceral arteriolar lesions were fairly constant among the animals and were almost invariably present in the heart, pancreas, testis and gastrointestinal tract. In the less severe forms of the



Fig 12 Arteriosclerotic lesion in testes

disease the vascular lesion both renal and general visceral was less impressive and less constant usually consisting of medial hypertrophy
Potassium Chloride (47-51)

The highly reproducible significant correlations of dietary salt with systolic blood pressure elevations and shortened life span in the rat offered a sensitive measure of potassium as an antagonist and possible interrelations of dietary sodium and potassium (35)

As you recall in 1843 it was postulated that the herbivores' treks to salt licks were motivated not by the lack of sodium in the diet but to the wealth of potassium (52). The fine report of Thompson and McQuarrie (53) in the early 1930s illustrates the hypertension governing effects of potassium chloride added to high sodium chloride diets in salt eating children (one as much as sixty-four grams daily). They stated: "In the case of one normal control subject the ingestion of fifteen grams of sodium chloride every six hours caused an increase in blood pressure from 115/80 to 118/100 mm Hg when the subject was on the simple relatively low potassium diet given to the three diabetic children but little or no change when he was taking an ordinary mixed diet containing liberal amounts of vegetables and meats." Priddle (54) in 1943 advocated potassium as a possible therapeutic agent in hypertension.

Experiments bringing the dietary K/Na ratio toward one were initiated in 1953. Concurrent control group and added NaCl groups comprised the

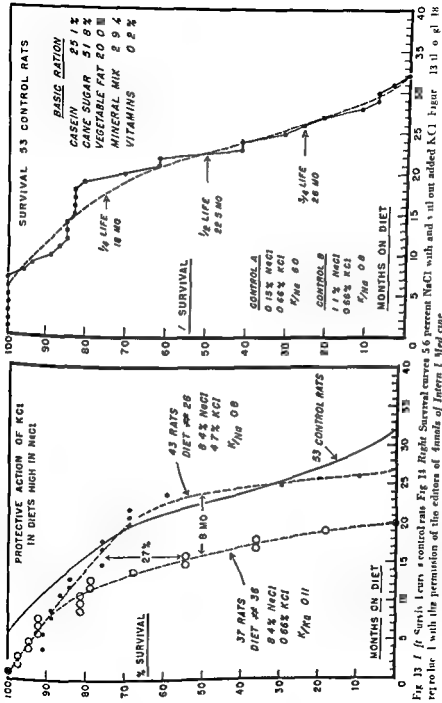


Fig 13 Left Survival curves a control rats Fig 14 Right Survival curves 5.6 percent NaCl with and without added KCl Figure 13 11 0 18
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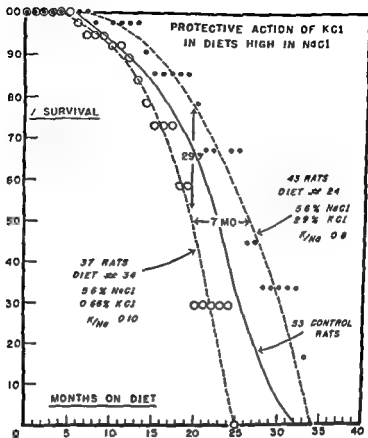
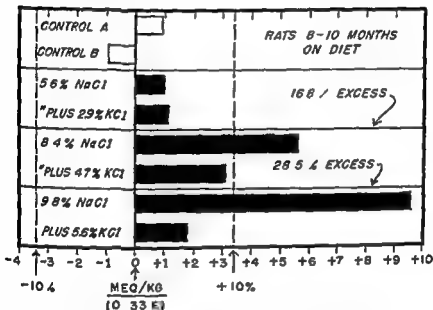


Fig 15 Survival curves 8.4 percent NaCl with and without added KCl

pilot experiment 56 percent NaCl + 29 percent KCl and 84 percent NaCl + 47 percent KCl were fed to the rat. The last experiment included rations containing 98 percent NaCl and 98 percent NaCl + 56 percent KCl. Let us look first at the protection afforded survival. At the 56 percent level of added salt bringing the K/Na ratio toward one enabled the consumers to outlive not only their counterparts but the concurrent control. Less dramatic but still significant was the difference at the 84 percent level. At 98 percent after early decimation by the nephrosis syndrome (the animals were probably approaching the total electrolyte limit) the potassium protected rats outlived their counterpart. After eight to ten months on the



TOTAL EXCHANGEABLE SODIUM, MEQ/KG ABOVE OR BELOW
CONTROL AVERAGE OF 33.6

Fig. 16 Total exchangeable sodium

regimen measurements of total body sodium by isotope dilution in selected rats showed some KCl protection at the 84 percent and definite KCl protection at the 98 percent level of sodium chloride.

Added potassium chloride had no apparent effect on the modest hypertension of rats fed at the 56 percent NaCl level. Blood pressure elevations were also present in the groups receiving 84 and 98 percent sodium chloride to which potassium was added but these did not approach either their

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DISCUSSION

DR HENRY A SCHROEDER I would like to bring out several important points First Dr Merrill would like to know the level of sodium and potassium in the plasma on the high salt diets Your control cholesterol values 130-140 are quite high for the rat in our experience and I wonder what method you used We find them usually around 100 or less

Secondly are not the lesions merely the nonspecific hypertensive vascular lesions you see in any form of hypertension?

The third point is that I think it hazardous to imply in any way a relationship between these morphological experiments and the situation in man Many measurements have been made on normal diet and urine and we believe five to eight grams per day is a normal intake of sodium chloride The measured intake in Japanese is ten grams which is less than the equivalent of the 28 percent level in your rat experiments and only a little more than in the American diet There is no evidence measurement wise that Japanese take larger amounts According to some old experiment eighteen grams per liter is the most a young adult apparently can concentrate in terms of sodium chloride Perhaps children can concentrate higher amounts older people concentrate less In Michigan some years ago Dr Richard Lyons

used thirty grams in young adults and got edema high venous pressure dyspnea and in some signs of cardiomegaly and pulmonary congestion whereas dogs can concentrate to levels many times higher. So I think we do not eat as much salt as is thought by Dr. Meneely, probably only four five or six grams. If you pour salt from a shaker into a spoon instead of on food you realize a gram goes a long way in seasoning food.

DR. E. D. FREIS: Some arterioles in the histological sections look like hypertensive changes and some like periarteritis nodosa. Selye produced periarteritis nodosa in rats. Did you see such lesions? Did you measure plasma volume or blood volume in any of these rats on high sodium diets?

DR. SIMON ROBBARD: In the experimental series that we reported yesterday we also fed cholesterol to some of the animals on a high salt diet. Our results show the addition of salt alone to animals on a normal mash diet changes neither the plasma cholesterol nor the tendency to atherosclerosis in the aorta or in the coronary vessels. However, addition of salt to the diet of animals receiving cholesterol definitely intensifies the lesions in the vessels even though the plasma cholesterol level is unaffected. I might also add that we saw no changes in the kidney comparable to those reported by Dr. Meneely. Perhaps this is due to species difference.

DR. SIDNEY FRIEDMAN: We find that if sodium is added to the diet in the absence of potassium the animal becomes severely hypotensive. In other words, sodium becomes a hypotensive agent in the complete absence of potassium in the diet. As Dr. Perera suggested, rigid restriction of potassium in the diet of essential hypertensive patients produces a moderate reduction in their blood pressure.

DR. GEORGE A. PERERA: About one quarter of that in the normal diet.

DR. ARTHUR M. FISHER: I would like to ask Dr. Meneely if the hypercholesterolemia in his experiments always accompanied hypoalbuminemia. A great deal of evidence has been brought out here about the role of increased sodium intake in the production of high blood pressure. But in treating human hypertensive patients on the ward one often observes that during heart failure they develop hyponatremia and nevertheless the hypertension persists at maximum levels. A patient may have a serum sodium of 110-115 milliequivalents for weeks with the blood pressure still at 200/120. This requires reconciliation with the conception of the relation of sodium retention to hypertension.

DR. GEORGE R. MENEELY: I feel like one of the chalcids of the Middle Ages. I think we have raised more ghosts than we have laid. I do not understand many of our findings. Our rats were given certain levels of sodium chloride; they chose to take certain amounts of fluid; and then certain things happened. The experiment is obviously too vast ever to complete the analysis. Therefore we can only regard it as a report of what happens in rats given this particular diet.

Obviously our animals were whole animals—they had all their parts. The classic example of the extirpation type of experiment concerns the man who said to a flea Jump flea jump. The flea jumped and he noted down that the flea can hear commands. After pulling the flea's legs off he yelled Jump and the flea did not jump. He then put down Removal of legs from fleas makes them deaf.

Dr Friedman we have never seen the blood pressure drift down in high salt eating animals—it always drifts up. That the rats wait seventeen months to manifest their difference from the controls suggests that whatever is going on is a slow process.

Dr Schroeder the blood levels of sodium and potassium are essentially normal. We do have some rather detailed analyses of organ sodium and potassium. The method of cholesterol level determination is that of Pearson and associates*.

This standard rat diet is high in fat and our rats get more calories from fat than we wish. I am sure the vascular lesions are nonspecific. I do not think there is periarteritis. We have not seen cellular infiltrate around the small arteries. These experiments may be unphysiological. They are of course on rats. I know nothing about man. Adequate figures for human intake of salt are some of the most needed and least known. My Japanese figure up to thirty grams of salt was pure hearsay. It is essential to find out how much salt people are eating.

Our sodium space findings are complicated. In waterlogged nephrotic rats sodium spaces ranged up to fifty or sixty percent of body weight with non edematous high salt rats having larger sodium spaces than controls. As life goes on the control sodium spaces go down somewhat while the others stay about the same. Meanwhile the non salt eating rats become obese. This may account for the differences. Venous pressure goes up in rats that develop heart failure.

Dr Rodbard I am very interested to hear about the salt and cholesterol effects. Our dogs are not becoming hypertensive but they are showing changes in cholesterol. With regard to the coincidence of hypoalbuminemia and hypercholesterolemia that is seen in the edematous rats.

*Pearson S, Stern S and McGauach T H

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J Clin Endocrinol Metab 17: 1245 1952

REPORT OF THE COMMITTEE ON INSTRUMENTAL TECHNIQUES

DR W F HAMILTON (Chairman)

DR H D GREEN

DR ERIC OGDEN

Criteria for the auscultatory measure of arterial pressure

In the last report of the American Heart Association Blood Pressure Committee (Circulation 5 503 1951) it was suggested that the cuff pressure at which sound was first heard as the pressure within the cuff was reduced be read as the systolic arterial pressure. In the appendix it was noted that the conclusion arrived at by four teams of workers after more than 100 comparisons with direct manometry is that the estimate of systolic pressure thus determined was too low by about three mm Hg. This correction was not made in the committee recommendations and has not been discussed insofar as we are aware in the recent literature.

The criterion suggested for the measurement of diastolic pressure however has received criticism because if for no other reason it has broken with tradition. The report cited above advises that the diastolic reading be recorded at the pressure level in the cuff where all sound stops as the pressure is gradually lowered. This is about 8 mm Hg below where sound muffles or fades and is found on comparison to be within a millimeter or two on the average of the true diastolic pressure. It is carefully pointed out that under hemodynamic conditions in which no cessation of sounds occurs the level of muffling should be recorded as a questionable diastolic reading.

This recommendation has been criticised as being unnecessarily complex and resulting in confusion in clinical reports in which the older (muffling) and the suggested criteria are not clearly distinguished.

It seems doubtful to the committee that any serious harm will be wrought by the effort for greater accuracy indicated by the report. Hemodynamic conditions (anemia, hyperthyroidism, aortic regurgitation) in which cessation of sound does not occur offer many other diagnostic signs than the auscultatory one. On the other hand the true level of diastolic pressure in hypertension is both uniquely important and more accurately measured by the cessation rather than by the muffling of sound.

Until a contradiction of data supporting this report is available and/or a theoretical basis is found for understanding the mechanism by which the Korotkoff sounds are produced it is suggested that the blood pressure pamphlet remain unrevised.

Blood Pressure Norms

It was suggested that your committee concern itself with blood pressure norms and minimal hypertensive levels. The competence of the committee does not extend to cover the broad statistical and clinical insight needed to cover this question adequately.

Technical difficulties and ambiguities should be in mind when comparisons are made with published or intuitively established norms. Thus on newborn infants agreement with directly measured umbilical systolic pressure is to be had by palpation only when the arm cuff is 2.5 cm wide. The conventional pediatrician's cuff gives figures 20-25 mm Hg too low. Unfortunately the published figures were obtained mostly with too wide a cuff and therefore are too low.

The opposite is true when cuff pressures are taken with standard arm cuffs in obese persons with large arms or in the thigh. It is best to look skeptically at cuff figures obtained on people with unusually large or small arms. The former are probably too high, the latter too low.

Ballistocardiography

This is a subject that is presently being considered by another committee of the American Heart Association.

Venous occlusion plethysmography is a technique which has been accepted intuitively because it seems reasonable. The history of physiological methodology confronts us with many programs which defaulted as soon as adequate examination of methodology was made. Much time has been given to getting and interpreting results by the venous occlusion method. It is highly desirable that this method be compared with other directly calibrated methods.

Skin temperature can be an index to blood flow only if environmental conditions such as humidity, air motion, air temperature and other factors can be thoroughly known and interpreted. The evaluation of the method again can come only from careful comparative experiments with a calibrated method for measuring blood flow.

Errors which might stultify the results obtained by the injection method for measuring blood flow through the lungs and other areas, or by the Fick procedure, must receive careful attention in the present rapidly changing of knowledge in this field.

Intravascular manometry

The use of a catheter or other flexible connection between a pressure transducer and the cavity whose internal pressure is to be measured is at best a makeshift. It is usually difficult and often impossible to place a catheter so that its intracardiac motion will not introduce pressure changes of inertial origin which cannot be damped out without stultifying the record. Getting a good intracardiac record of pressure is a matter of good luck rather than good management with present equipment. Getting a good record from a bad one is a problem that requires considerable insight and for which a rule of thumb is not at present available.

It seems that we are awaiting the marketing of one of the several proposed transducers that can be made independent of all hydraulic columns by having its electrical parts on the end of the catheter. Hazards involved in this approach, among others, are that the transducer may work loose and come off inside. Whether this hazard is greater than that of having a knot form

in an ordinary catheter is questionable. It may be hard to establish a stable known zero with certain models of intracardiac transducers but a recently developed model overcomes this difficulty by allowing simultaneous external registration of mean pressure through the lumen of the gauge.

The agreement of investigators as to the hydrostatic level to which pressures should be referred is a goal to be sought. A good case can be made for the hydrostatic level that is basic to the function or role of the pressure concerned. Thus pressures in the venous system which fill the right ventricle should be considered in relation to the height of the right ventricle or the apex beat and pressures whose role is to distend and cause filtration in the capillary bed should be considered in relation to the mean height of the capillaries themselves.

However the investigator refers his pressures both he and the editors of journals should be urged to see to it that the frame of reference should be explicitly stated so that another investigator may calculate his results to a comparable frame of reference. Thus when venous pressures are under consideration a figure of say 10 cm H₂O is quite meaningless. Additional data should be given: 1) landmark for zero; 2) the position of the animal or subject (prone, supine or lateral) and 3) the dimensions of the chest.

It should also be realized that in practically all situations including calculating resistance to flow the arterio-venous pressure difference is important while arterial pressure alone may be meaningless. In studying factors which produce congestion and capillary filtration transmural pressure is important and may in the presence of appreciable ambient pressures be quite different from intraluminal pressures. The low ambient pressure in the thorax and the high ambient pressure during the contraction of the walls of the uterus or of the abdomen should be specified where relevant.

REPORT OF COMMITTEE ON CHEMOTHERAPY IN HYPERTENSION

DR M MENDLOWITZ (Chairman)

DR J BORDLEY III

DR S W HOOBLER

DR E D FREIS

DR C THOMAS

The purpose of this report is to indicate the present status of chemotherapy for hypertension with the full realization that the field is controversial and still developing. No statement as to indications for dosage or value of any therapeutic agent is therefore meant to be dogmatic or final. Antihypertensive treatment with drugs is often used in a wide spectrum of hypertensive disease. The chief objective of such treatment is the prevention of subsequent structural vascular disease with consequent organ impairment chiefly in the brain, the eyes, the heart or the kidneys. A secondary objective is the amelioration of such symptoms as may properly be attributed to the hypertension especially various grades of hypertensive encephalopathy and of left ventricular failure.

There is considerable agreement concerning contra indications to drug therapy but a wide divergence of opinion as to indications. Uremia with severe nitrogen retention is generally considered to be a contra indication to treatment. With mild nitrogen retention antihypertensive treatment may improve renal function in some cases but this should be carefully followed with daily blood urea nitrogen determinations. There are exceptions to this blanket rule especially if the blood urea nitrogen be elevated on the basis of an *intercurrent reversible process* such as *pyelonephritis*, *lower nephron nephrosis* or *congestive heart failure*. Hypertension in the aged is usually considered not to be amenable to aggressive treatment although again this is true only if the hypertension is largely systolic and hence on an arterio sclerotic basis. Some elderly patients in whom it can be demonstrated that the hypertension is neurogenic or with evident vascular acceleration may be treated. Hypertension secondary to renal and vascular diseases such as acute and chronic glomerulonephritis, amyloid contracted kidneys, polycystic kidneys, lupus erythematosus, periarteritis nodosa, diabetes mellitus, Goldblatt kidney, coarctation of the aorta, etc. are ordinarily not considered amenable to antihypertensive treatment. There are many exceptions to this rule however and each case therefore deserves evaluation. If the hypertension is excessive therapeutic trial is justified. Acute coronary occlusion or acute cerebrovascular accident are generally contraindications whereas residuals of the events are not necessarily contraindications to antihypertensive treatment. Angina pectoris may be improved or made worse by treatment and each case must be evaluated separately.

There is some agreement as to indications for treatment but also large areas of discord. Most observers are agreed that the accelerated form or the so called malignant phase of essential hypertension must be treated vigorously. Nearly all workers also favor vigorous treatment of hypertensive crises or encephalopathy especially if relatively uncomplicated by uremia. There is a wide divergence of opinion however as to whether uncomplicated essential or primary hypertension should be treated at any age. There are some who believe that since such people may be asymptomatic for many years and never develop accelerated hypertension they should not be subjected to the hazard, expense and discomfort of treatment whereas others believe that all hypertension accelerates vascular disease and that early treatment is therefore important.

Most workers in the field are agreed that except where treatment should be prompt and vigorous as in malignant hypertension some form of rauwolfia derivative is the drug of choice with which to begin antihypertensive treatment. The results are generally better with reference to the hypertension than if a more general sedative such as phenobarbital is used. There is little difference between the various forms of rauwolfia drug provided the dosage is standardized and adjusted in each case. The suggested initial dose of reserpine for example is 0.25 mg. three times daily. Doses greater than this are not of additional value and increase the side actions whereas smaller doses (0.1 to 0.25 mg. once daily) often can be employed for maintenance of effect. If the

rauwolfia drugs are not effective in any given case they should be withdrawn but effective reductions in blood pressure can be achieved with rauwolfia alone in many cases of hypertension. Side actions of the rauwolfia drugs consist of occasional diarrhea and nausea, nasal stuffiness, blurring of vision, fluid retention with edema, untended gas, a tendency toward frightening dreams and most important depressive psychosis. The latter reaction which may be preceded by agitation and insomnia is often a late effect following four months to three years or more of rauwolfia therapy. It is always a contraindication to continuing therapy. The other symptoms can be met by dosage adjustments and in the case of nasal obstruction by supplementation with antihistaminic drugs and vasoconstrictive nose drops. Occasionally peptic ulcer is produced or activated by rauwolfia drugs and this may be manifested by pain or by a tarry stool or hematemesis. In such cases the drug should ordinarily be discontinued. Epilepsy is considered a contraindication to rauwolfia on theoretical grounds but clinical evidence of its harmfulness is as yet incomplete.

Veratrum derivatives may be used to supplement rauwolfia on occasion but have been found by many observers not to be very useful for this purpose. If there is tachycardia and a contraindication to rauwolfia, veratrum is useful as a substitute. It has the disadvantage of the rapid development of tolerance and of the side actions of nausea and vomiting which often appear close to the therapeutic dose level. As a prototype the oral dose of protoveratrine A and B is 0.4 mg spaced six hours apart with the added precaution that no food be ingested for four hours after any single dose. Dosage may be increased gradually until there is either a satisfactory reduction of blood pressure or the appearance of nausea and vomiting.

Hydralazine is a useful supplement to rauwolfia and may also be given independently. There are many side actions of the drug including headache, nausea, vomiting, drug fever, rash and fluid retention. The most serious side action is a lupus erythematosus like reaction with arthropathy, skin eruption, fever and a positive L.E. cell test. This is less commonly seen if a dosage of 400 mg daily is not exceeded and rarely occurs on a dose of 200 mg daily or less. Many side actions can be avoided if the dosage begins at 10 mg three times a day and is thereafter gradually increased and if rauwolfia is administered for several weeks prior to the exhibition of hydralazine. Angina pectoris is a contraindication to the use of hydralazine and tachycardia and even angina itself may be induced by the drug in some cases.

The ganglion blocking drugs may also be used independently or in combination with other drugs. There seems to be little choice between the various preparations: mecamylamine, chlorisondamine or pentolinium. Mecamylamine has the advantage of complete absorption after oral administration but the disadvantage of prominent side effects due to parasympathetic blockade. Dosage of these drugs should begin quite low and be gradually increased. The initial twice daily dose of mecamylamine is 2.5 mg, of pentolinium 20 mg and of chlorisondamine 25 mg with gradual increase in amount and/or frequency until

an adequate effect is achieved or until intolerable side actions preclude further increase. Coarse tremor and psychosis have been side effects of very large doses of mecamylamine given to patients already in uremia or with cerebrovascular disease.

Successful use of the ganglion blocking agents requires detailed knowledge and special effort. Dosage must be titrated to the individual requirements of each patient. Some physicians prefer to use home blood pressures in the standing position for this purpose since office blood pressures are often falsely high whereas others do not favor home blood pressures because of the anxiety they create and the inconvenience involved. If office blood pressures are used it is better that they be taken by the office assistant or nurse both in the erect and in the supine positions. If it is suspected that they are falsely high the attempt to reduce the erect blood pressure to completely normotensive levels need not be pressed.

The complaint of dizziness or faintness on standing relieved by recumbency is usually a good indication that dosage should be reduced regardless of the recorded office blood pressure. This symptom however must sometimes be distinguished from the dizziness produced by the hypertension or by labyrinthine disease. Dosage may require adjustment because of increased reactivity to the drug which is induced by hot weather, the ingestion of alcohol or by acute salt loss.

The physician needs to be familiar with the common side effects of sympathetic blockade such as postural syncope or faintness, chilling in a cold environment, increased susceptibility to heat stroke, and of parasympathetic blockade such as dry mouth, disturbance in visual accommodation, gastrointestinal atony, impotence and difficulty in emptying the urinary bladder. A rare peculiar type of interstitial pneumonia has been attributed by some workers to hexamethonium whereas others believe this to be uremic pneumonitis not related to the administration of the drug. Many of the side effects do not occur with careful dosage regulation and when they do occur they are often transient. Some of the side effects can be circumvented by the use of parasympathomimetic agents such as pilocarpine and neostigmine. Cathartics and enemata are almost always necessary to combat the constipation often seen. In fact constipation is so common that cathartics are usually given with the initiation of treatment. The degree of success achieved with the ganglion blocking agents depends in large measure on the skill and patience of the physician and the intelligence and fortitude of the patient.

Other drugs which are often used in the management of hypertension are the barbiturates and the tranquilizers including thorazine, meprobamate and their derivatives. They are useful for allaying anxiety especially if there is a contraindication to rauwolfia but produce little if any lowering of blood pressure *per se*.

Mercurial and other diuretics are useful supplements to the low sodium diet especially for the treatment as well as the prevention of left ventricular failure.

and any of the drugs discussed in this report may be used in conjunction with the 200 mg low sodium diet provided the blood urea nitrogen concentration is checked frequently and the silent development of renal insufficiency is avoided. A recent development has been the discovery that chlorothiazide a diuretic and potent saluretic agent will reduce blood pressure in hypertensive but apparently not in normotensive individuals. Experience with this drug is still too limited to make definitive claims for it. The drug will however potentiate the action of ganglion blocking agents. One half gram on arising and at bedtime is the ordinary maintenance dose. Although chlorothiazide appears to have promise the possibility of sodium chloride or potassium depletion or progressive azotemia must be kept in mind. In addition enough time has not elapsed to judge the effects of this agent in the treatment of hypertension or to be certain of the absence of long term toxic effects.

Hypertensive encephalopathy requires special treatment with drugs whether it occurs in pregnancy as eclampsia or in the patient with advanced hypertension. There is some question in eclampsia whether such treatment increases fetal mortality. Antihypertensive therapy is usually begun at once especially if the blood urea nitrogen level is below 60. Since there is often psychic obtundation barbiturates are contraindicated. Because vomiting is common drugs should ordinarily be given dissolved in five percent glucose and water solution by intravenous drip. Those most commonly used for this purpose are protoveratrine and trimethaphan (Arfonad®). An alternative procedure if continuous measurement of blood pressure is impractical is to give five mg of reserpine intramuscularly. When the sensorium has become clear and vomiting has stopped transition to oral treatment may be effected. During drug infusion blood pressure should be brought down to no lower than 170/90 by adjusting the dose of the drug and the rate of infusion.

The committee wishes to emphasize that no two cases of hypertension are alike and that therapy must be considered an individual experiment in each case. Thorough clinical evaluation before treatment is mandatory especially in the severe cases. It should also be remembered that the use of drugs is only one aspect of the total treatment of hypertension.

REPORT OF COMMITTEE ON SURGICAL TREATMENT OF HYPERTENSION

DR EDWARD FREIS Chairman
DR WILLIAM COLDRING
DR KEITH CRIMSON

The surgical treatment of hypertension includes procedures aimed at eradication of primary etiologic processes such as (1) unilateral renal disease circulatory ischemia or hypoplasia (2) adrenal hyperfunction due to cortical adenoma carcinoma or hyperplasia (3) pheochromocytoma and (4) coarctation of the aorta. In these conditions surgical intervention is indicated providing

the patient's general condition permits and the damage has not become so far advanced as to preclude successful results of such intervention

There is marked variability of opinion concerning the value of sympathectomy in hypertension. However, most of the long term follow up reports in the literature suggest some prolongation of life. The difficulty in a truly definitive evaluation of reports is the lack of adequate control series followed concomitantly with the treated series. Comparison of surgical results with various series treated medically by other individuals in different locations and at other times always is open to some question.

The ability to select favorable from unfavorable responders prior to surgery is the main problem. Sympathectomy probably is best indicated for patients under the age of fifty to fifty five who exhibit evidence of acceleration but without marked renal impairment (phenol sulphphenphthalein excretion greater than fifteen percent in fifteen minutes and no azotemia). The operation definitely is not indicated for patients with nitrogen retention. They have not tolerated surgery well and those who survive the postoperative period rarely have shown evidence of retrogression of their disease. Patients with a slowly progressive hypertension could have sympathectomy as an elective procedure.

It is the prevailing opinion that an adequate trial of anti hypertensive drug therapy including the use of ganglionic blocking agents should be undertaken prior to advising surgery. However, if the trial is unsuccessful in controlling blood pressure levels or in arresting the progress of the disease as shown by failure of clearing of hemorrhages, exudates or papilledema in the optic fundi, episodes of hypertensive encephalopathy or increasing cardiomegaly and albuminuria, sympathectomy may be recommended. Some authorities believe that if a patient does not respond to blocking agents he also will not respond to sympathectomy. Others believe that this is not always the case and also that there are patients who do not cooperate well enough for a long term medical program to be effective.

The most practical type and extent of sympathectomy will vary with the training and experience of the surgeon and the severity of the disease. Splanchnicectomy includes removal of the lower thoracic and the upper or all lumbar ganglia with the splanchnic nerves and with or without removal of the celiac ganglia. Total sympathectomy includes this and also removal of the stellate and upper thoracic ganglia to denervate the cardiopulmonary area and the upper body. This produces slowing of the heart rate. Vasoconstrictor pathways through the second and third lumbar ganglia usually are not removed. The purpose is to avoid incapacitating postural hypotension. As determined by sweat and skin resistance tests, some return of sympathetic nervous activity occurs a year or more after operation. Removal of intermediate ganglia such as the iliac and the stellate minimizes functional regeneration.

In general the more extensive the sympathectomy the more likely it is that there will be a lasting and significant reduction in blood pressure. However, the length of the period of postoperative disability and the occurrence of

complications of surgery also may be increased in proportion to the extent of sympathectomy. This increased risk and disability may be justified in rapidly advancing or in chronic and intractable cases.

Total adrenalectomy for hypertension has not been sufficiently well evaluated to warrant use other than as an experimental procedure. It has not yet been proved that survival is any greater. The same may be said for the combined procedures of sympathectomy and total or partial adrenalectomy. The evidence available indicates that these procedures also have been unsuccessful in the presence of marked renal impairment.

The principal disadvantage of sympathectomy is the inability to select with any assurance the patients who will achieve long term reduction of blood pressure. However, postural hypotension and relief of symptoms is more frequent than reduction of supine pressure. Since the advent of more effective antihypertensive agents the number of sympathectomies done in most medical centers has decreased markedly. One advantage of the surgical approach, however, is that it does not require meticulous and indefinitely protracted medical management such as is required with either dietotherapy or treatment with most antihypertensive agents. Whatever lasting protection is achieved by sympathectomy is not entirely dependent on the patient's will to cooperate; the protection obtained with a medical regimen lasts only as long as the patient desires to continue his treatment. There is also some evidence to suggest that after sympathectomy the patient's blood pressure may become more responsive to the various forms of medical treatment.

A few authorities do not believe that mere reduction of blood pressure, either by sympathectomy or by the use of antihypertensive drugs, has been proved to be of any real value either in preventing complications or prolonging life. Since long term statistically definitive controlled studies are lacking it is impossible to settle this issue one way or the other. Nevertheless, the majority opinion of this council is that hypertension accelerates vascular changes and that as a rule reduction of blood pressure promotes increased longevity. Thus, if a patient is a candidate for sympathectomy, if he fails to respond to antihypertensive drug therapy or will not tolerate a long term medical regimen, and if he is willing to accept surgery for its possible benefit, sympathectomy may be advised.

REPORT OF COMMITTEE ON EPIDEMIOLOGY OF HYPERTENSION

DR KENNETH KOHLSTAEDT, Chairman

DR ARTHUR FISHERG

DR LEVIN WATERS

DR ARTHUR MERRILL

DR EDWARD WEISS

The application of epidemiological methods to the study of hypertension offers an opportunity to obtain information that will be useful in establishing the cause of primary diastolic hypertension and thereby aid in eliminating this

di order Studies should not be undertaken without guidance of persons trained in epidemiology

In considering areas for future investigation this committee proposes that the factors be divided into three categories on the basis of need for information and practicability of study

1 In the first group are a number of problems which in our opinion have already received adequate consideration and concerning which it is doubtful that additional studies would be of value

Race—It is well known that hypertension is frequent and often severe in the Negro. It is difficult to separate race from heredity and environment in the course of an epidemiological study. It is likely that in the future racial background will become less important.

Obesity—In the past being overweight has been considered a cause *per se* of high blood pressure. The committee wishes to point out that errors in measuring arterial pressure by the auscultatory method on the very large upper arm of obese persons may have been responsible for the establishment of this concept. The reduction in blood pressure attributed to loss of weight may actually have been due to improved accuracy in recording pressure when the circumference of the arm was decreased. The false correlation of obesity and hypertension can be eliminated by wrapping the cuff of the sphygmomanometer around the forearm and estimating the systolic pressure by palpating pulsation of the radial artery as pressure within the cuff is decreased.

Body build and height and use of alcohol or tobacco—In the opinion of the committee there is sufficient evidence to justify the conclusion that none of these are concerned in the genesis of primary diastolic hypertension.

Food—At the present time there is no evidence that food itself is a factor in elevated arterial pressure. There is no basis in fact for the once popular belief that red meat was harmful to persons with hypertension.

Physical exercise—Moderate physical exercise is not considered harmful for patients with primary diastolic hypertension. The committee does not believe that investigation of physical activity deserves further consideration in an epidemiological study.

2 The second category is composed of factors that may be important but which should be difficult to study.

The effect of age—Although evidence has shown that there is a difference between blood pressure in children and in adults and that there is a tendency for arterial pressure (especially systolic pressure) to increase as the individual grows older, a study of age in relation to the development of primary diastolic hypertension would require numerous longitudinal studies (observations extending over a prolonged period). This form of investigation is very costly. The committee believes that observations made by Hamilton, Pickering, Roberts and Sowry (Clim. Sc. 13:37, 1954) indicate the problems to be expected in obtaining information regarding the relationship between age and blood pressure. The data presented by the investigators do not warrant the con-

clusion that primary diastolic hypertension may be a phenomenon of aging rather than of disease. The relationship between age and blood pressure is admittedly a very complex problem that would be difficult to study by epidemiological methods.

The role of emotional stress—A personality pattern characteristic of primary diastolic hypertension has not been defined. There is insufficient evidence to support the concept that emotional stress causes hypertension. A study of the role of emotions in the elevation of blood pressure would be a formidable undertaking. Normotensive controls would be needed. Adequate tests for emotional factors are not known and even if they were it is doubtful if a sufficient number of trained persons would be available to conduct them.

3. In a third category the committee considered the factors that are believed to be important in the genesis of hypertension and that should receive priority.

Heredity and environment deserve the immediate attention of investigators. The measurement of blood pressure in relatives of patients with primary diastolic hypertension can be done without great expense and if properly executed a great deal of useful information could be obtained in a short time. Another worthwhile study would be the recording of blood pressure in a large number of twins. Measurement of blood pressure in large populations also might shed light on the relation of sex to the pathogenesis of hypertension.

A study of environmental factors would be more difficult than problems related to heredity. An epidemiological investigation if carefully controlled could be of great value in elucidating the effect of environment on the occurrence of hypertension. At this time the role of sodium as an environmental factor in the genesis of primary diastolic hypertension is of paramount importance. Although epidemiological studies of the dietary habits of a population are difficult, a thorough investigation of the relation of both the sodium and potassium content of food and water to the incidence of high blood pressure and vascular damage would provide a great deal of useful information.

It is the opinion of the committee that the evaluation of tests for hyperreactivity of the vasomotor system could be the subject of study. There are no satisfactory ones available at the present time. The committee hopes investigators will give attention to this problem.

Time did not permit a full discussion and review of this report at the November 1957 meeting of the Medical Advisory Council. It is hoped the epidemiology of hypertension may receive further consideration at future meetings.

The committee wishes to thank Dr. John W. Ferrer, Associate Medical Director of the American Heart Association, for his help in providing information.

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SURGERY FOR HYPERTENSION AND RELATED CARDIOVASCULAR DISEASES

KEITH S. GRIMSON, M.D.

*Department of Surgery Duke University School of Medicine
Durham, N. C.*

The earliest form of surgery for high blood pressure was a limited sympathectomy — splanchnicectomy. The sympathetic nerves activate or regulate the blood vessels and blood flow throughout the body. The splanchnic branches in particular supply the abdominal viscera. Splanchnicectomy had been first theoretically considered by French physicians. It had then been performed in this country by Adson Peet and other surgeons between 1930 and 1935. Surgical research on high blood pressure and interest in the sympathetic nervous system was in part a logical outgrowth of studies on low blood pressure or shock stimulated by the high mortality rate among the wounded between 1914 and 1918. Cardiovascular discoveries and their application to clinical problem have continued steadily until now cardiovascular surgery is almost a specialty.

In general there are two types of surgical approach to hypertension. One is the removal of nerves, organs or glands whose normal function is detrimental to a hypertensive patient. The other attempts repair or replacement of diseased or worn out structures of the body. All operations are based upon knowledge of structure and function of the body and of the mechanisms causing high blood pressure.

The cause of hypertension is differently emphasized by the followers of two classical schools of thought. One began here in Cleveland in 1933 when Dr. Harry Goldblatt demonstrated that partial obstruction of the arteries to the kidneys caused hypertension in dogs. Dr. Irvine Page carried on some experiments to demonstrate that the culprit was angiotonin, a substance released into the blood stream by the obstructed kidney. Surgically this concept has led through various research steps to clinical application in the occasional cure of hypertension by the removal of one diseased kidney. Within the last two years several groups have used x-rays of the arteries to the kidney to demonstrate small points of obstruction and have repaired the defect or have removed one kidney. Results are not always encouraging. Why not remove both kidneys for patients with renal hypertension? First the patient would not live long. Second Dr. Arthur Grollman and others have shown that an insufficiency of kidney tissue can also cause high blood pressure, the so-called renoprival hypertension. This in a sense is the opposite of the Goldblatt theory. Similar difficult problems have to be faced in experimental and clinical attempts to bring a new blood supply to a kidney. Interruption of the nerves to the kidney has not helped. Research is continuing but as yet there is no reliable surgery on the kidneys for most patients with this form of high blood pressure.

The second classical school of thought centers around the work of Professor C. Heymans and his proof that hypertension could be caused in dogs by dividing the nerves from certain pressure sensitive areas of the arteries of the neck and heart. These normally act as governors to keep blood pressure down to normal levels in anger, frustration, etc. In patients with this common form of hypertension the buffering mechanism still functions although reset at a higher pressure level. We do not yet know how to readjust the pressure setting. However, removal of *all* of the sympathetic nerves in animals with this neurogenic hypertension restores blood pressure to normal by disconnecting the nerve wiring circuit at its most accessible point. Is it necessary to disconnect the sympathetic nervous system completely? Many experiments indicate that it is. Half a sympathectomy does little in animals. The sympathetic nerves to the head and heart are just as important in the maintenance of neurogenic hypertension as are those to the kidneys and abdominal viscera. The operations of Adson and Peet and their subsequent modification by Smithwick in 1939 were planchnicectomies focused on the kidneys and abdominal viscera only. These operations effect some relief of symptoms and an occasional definite reduction of blood pressure. Many surgeons now employ modifications of the original procedure but still limit their operation to a planchnicectomy.

Because of training with Heymans' experiments in animals and a belief that neurogenic components of the hypertensive disease process are important *initiating and perpetuating factors*, I started total sympathectomy in 1940. This operation includes denervation of the upper body and thoracic viscera as well as the planchnic area. Results among 220 patients so treated have been encouraging, with maintained reduction of blood pressure to about normal in a third, reduction but not to normal in a third, and relief of symptoms and apparent increased life expectancy for most. These results added to those from the use of new drugs which suppress the sympathetic ganglia demonstrate the significance of the neurogenic component of hypertension. Even the present popularity of the so-called tranquilizing drugs is evidence of this. There seems to be no doubt that suppression of the sympathetic nerves by drugs or surgery is at present the most practical way of benefiting patients with hypertension.

Removal of the adrenal glands is another form of surgery directed at reducing blood pressure by interfering with structures which have apparently normal function. Patients with loss of these glands by disease suffer from low blood pressure and may require Cortisone to keep them alive. Experimentally and clinically it is difficult to produce a compromise or balance between the evils of high and those of low blood pressure. If the adrenals are totally removed and then adequate doses of Cortisone are given, hypertension returns. For this and other reasons, total adrenalectomy has not become popular. Research in this field continues. For the present, the accepted form of adrenalectomy is the removal of a rare tumor, a pheochromocytoma.

toma which secretes adrenalin and does cause a hypertension that can be corrected. For the last five years Dr. Harold Zintel and his associates have felt it necessary to remove part of the adrenal glands to reinforce the effects of splanchnicectomy. Removal of ninety five percent of the adrenals may be too much for one patient not enough for the next. This leaves most patients in constant need of medical supervision and Cortisone. This operation has met with limited trial and popularity. Sympathectomy, renal surgery and adrenalectomy have been the main surgical approaches to hypertension by altering normal function.

Repair or replacement of body structures is usually directed toward a main complication of hypertension: hardening of the arteries or arterio sclerosis. Common causes of death from high blood pressure are damage to the brain, heart and kidneys by coexisting arterio sclerosis which is accelerated by the high pressure. Today the recognition of the importance of low fat diet and of the use of sitosterols such as Cytellin in the prevention and management of arteriosclerosis probably will improve results of all forms of treatment of hypertension and will minimize these complications.

The arteries to the brain can be damaged by arteriosclerotic obstruction of the flow of blood (minor strokes) by sudden occlusion from a blood clot (thrombosis) or by rupture and hemorrhage. Dr. Champ Lyons and others have demonstrated small segments of occlusion of the carotid arteries in the neck and have removed the segments replacing them by cloth tubes or by arteries from an artery bank. Also the obstructions can be cleared out from within the artery — thrombo endarterectomy. This benefits patients having repeated small strokes. Patients losing consciousness with the sudden development of a thrombosis within the skull have been given injections of novocain into the upper sympathetic ganglia to try to reduce spasm of collateral vessels and improve circulation. This minor operative procedure may have helped some patients. However there is evidence that the blood vessels of the brain enclosed as they are in a hard skull have little sympathetic control. Probably one of the most important relatively new developments has been the use of cerebral angiograms to demonstrate by x-ray the presence of small aneurysms or ruptured vessels in patients who have had a cerebral hemorrhage and are about to have another. Neurosurgeons can operate in the neck applying a clamp to decrease pressure and then operate within the skull to remove clip or tie off these aneurysms.

The coronary arteries to the heart can also gradually occlude or suddenly thrombose causing disability or death to our hypertensive patients. Most of the research and the clinical advances in cardiac surgery today have been in the field of congenital abnormalities in children and in treatment of valvular diseases usually rheumatic in origin. The techniques for heart lung pump for topping and starting hearts and for operating upon open bloodless heart chambers are available for the management of coronary diseases. However there is an associated mortality risk even in young patients with

out coronary disease and to the best of my knowledge this type of cardiac surgery has not been applied to the greater risk patient — the older man with coronary insufficiency and angina

Early surgical efforts with coronary disease both experimental and clinical consisted of introducing irritating substances to cause inflammatory reactions in the sac or space about the heart which is called the pericardium. Also tried were the attachment of lung, abdominal omental fat, or other structures to the heart. In the early stages of healing inflammatory tissue at the site of a foreign substance is vascular. Later it tends to become relatively avascular cartilage. Dr. Claude Beck in Cleveland has long worked with the blood flow through the coronary sinus and has devised several operations designed to develop intercoronary communications to increase blood flow. His latest operation is a simplification of the earlier ones designed to reduce mortality risk. He abrades the walls of the heart and its pericardial sac in places powdered asbestos and partially ligates the coronary sinus. This procedure has been tested both in animals and in man. Another operation developed several years ago by Dr. Arthur Vineberg of Montreal is the moving of the internal mammary artery from its location beneath the breast bone or sternum into a tunnel in the wall of the heart. Experiments indicate that new arteries can branch out from this transplanted vessel. A direct approach to clean out or replace obstructed segments of coronary arteries was reported from Minneapolis by Doctors Absolon, Aut, Varco and Lillehei in 1956. Early this year Dr. Charles Bailey of Philadelphia reported removal of the thickened lining of a coronary artery in two patients. He used a special instrument to scrape or ream out the deposits which clog it. These operations require a general anesthetic and surgery on the surface of the beating heart. A procedure which does not was developed by Dr. Robert Glover of Philadelphia within the last few years. This is the ligation of the internal mammary artery. The artery is easily accessible for ligation. Because of its simplicity this operation has been employed frequently but there is extensive debate about rationale and results.

Experimentally a great deal of work is progressing along all of these lines. Why is it then that I can ask for a show of hands by physicians in this room and probably find an overwhelming majority who do not advise any surgery for the great majority of coronary patients?

There are several medical reasons but the most important seems to be that it is hard to know whether there is any improvement after surgery or at least sufficient improvement to warrant the operative risk. Perhaps ninety percent of good risk patients survive their initial myocardial infarction. With improved methods of medical treatment more than one half of the survivors live longer than five years and one third ten years. Many patients live to beyond the ten years and would be considered a good result had they had an operation. Surgical patients are necessarily selected and therefore

constitute a somewhat different population from those receiving medical management. I can only say that a popular operation for coronary insufficiency has not yet evolved and that generally accepted proof of the value of this surgery has not yet been presented. However, I can assure you that this is a problem which is receiving extensive investigation and increasing clinical trial.

My medical colleagues here are probably wondering whether I have overlooked the role of surgery of the autonomic nervous system in the treatment of patients with coronary insufficiency. The subconscious vegetative or autonomic nervous system has two main divisions. One is the sympathetic. The other is the parasympathetic with its vagus nerves to the heart. The vagus nerves slow the rate of the heart. The sympathetic nerves accelerate the heart and also conduct pain sensations from the heart. All of my sympathectomized hypertensive patients have a slow heart rate and should experience no coronary pain. It has been reassuring to observe that these completely sympathectomized patients, who without surgery should have had a high rate of coronary difficulty and angina, have instead a low incidence of cardiac trouble. I wish I could persuade more of my surgical colleagues to include this cardiac denervation with their splanchnicectomies for hypertension.

It is today a generally accepted theory that occasional patients disabled by severe angina can be relieved by sympathetic denervation of the heart. Several surgeons have removed both the vagus and sympathetic to the heart as the e nerves join in the cardiac nerve plexus. Here again the balance between risk and benefit is difficult to establish.

The large artery of the body, the aorta, and its largest branches can obstruct or dilate and form aneurysms in patients with hypertension as well as arteriosclerosis. Successful replacements and clean out procedures have been devised and are commonly applied. Greater difficulty is encountered in the main arteries to the legs and arms but percentages of success are encouraging. The smaller arteries of the body, such as the coronary arteries, are seldom successfully treated by direct arterial surgery. Generally, as the size of blocked arteries decreases from the aorta out through its branches to the extremities, a regional sympathectomy becomes the operation of choice.

Replacement of organs is a difficult problem. I know of no one who has suggested replacing the brain. Some Russian scientists postulated and tried in animals replacement of the heart. Substitution of a kidney is more logical and American. The artificial kidney developed by Dr. Willem Kolff and Dr. Jack Leonard of Cleveland, Dr. John Merrill in Boston and others, have proved a practical method for supporting patient with temporary renal failure. Until two years ago the transplantation of the human kidney from a healthy individual or body to a patient has met with failure or only temporary survival just as happens in dogs. Two years ago Dr. Joseph Murray and Dr. Hartwell Harrison of Boston successfully transplanted a normal kidney from a normal identical twin to his brother who was dying because of

to s of function of his kidney. This achievement has again stimulated research directed toward the immunological and other aspects of tissue transplantation in an effort to make this feat possible for patients who are not identical twin. The barrier which has prevented successful organ transplants from one person to another now is cracked and weakened although still strong.

THE WAY TO A MAN'S HEART

GEORGE A. PERERA, M.D.

Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York

A few years ago a wealthy banker approached me and said: "I have read all the scientific and medical literature and am convinced it is possible for you to keep me alive until I am 110 years old." His financial offer for such a program was most tempting but I turned him down. He presents what is today a growing epidemic of fear and anxiety. There are few who choose to remember that life is fatal and that the only really successful way to prevent old age is to commit suicide when one is young.

There is considerable talk about nutrition and vitamins and how they produce bigger and better babies, healthier children, bigger hoers and taller basket ball players. On reaching adult life in contradistinction one is advised to do without wine, women and song, in order to stay alive and avoid heart disease. When you go to a surgeon to have a gall bladder or other spare part removed, the good doctor thinks about a lot of things. He asks himself whether an operation will relieve symptoms and whether it will cure the trouble. What are the risks? How much will the patient be disabled? Are there other ways of solving the problem? Is the patient willing to go through an operative procedure? Will he cooperate? What are the psychological consequences? The same can be true of diets; if carried to extremes they too can induce restrictions and alter the way of life, be expensive and produce all sorts of emotional adjustments. In fact similar to drugs or surgery they can cause harm through nutritional deficiencies and in other ways.

The title of this talk is "The Way to a Man's Heart." I do not know whether a young lady is taught how to cook these days but that supposedly used to be the way she got her man. If he cooks too well it is said that she will get her man's inuence. Cupid's arrow becomes transformed to the barbed arrow of diet delivering its sting through too much salt, too many calories or too much fat. These are the ingredients which have received much attention in the fields of hypertension and atherosclerosis.

I should like to confuse you briefly and air a few representative examples of medical knowledge and lack of knowledge. This will not be a complete story but just a few tales about salt, obesity and fat. As one of you heard this morning, there is considerable evidence that if we reduce the amount of salt in our diet, deleterious effect of high blood pressure may be lessened. Lowered salt intake may lower the pressure level a little in some patient.

relieve symptoms and help a few of the complications. Diets that are very restricted may lower the amount of cholesterol in the body. But now let us ask ourselves a few questions. It is not established that taking away the salt in the diet cures the patient. In fact it is rather hard to convince ourselves that the life of the patient is lengthened to any material extent. There is little knowledge yet of the mechanisms by which low salt diet exerts beneficial effects. When the level of cholesterol drops in the blood where does the cholesterol go? There is a remote possibility that it may go into the walls of the blood vessels just the place we should like to avoid. When the cholesterol decreases after a low salt diet certain other fatty substances in the circulation are increased. There are many remaining questions as you can see.

What about being overweight? You have heard this story before. Doctors do not like their patients to be overweight. No one recommends that you go upstairs carrying a lot of suitcases and if these are built in suitcases you should logically make the load less by cutting down your weight. We know that certain complications of disease are more difficult to treat in patients who are overweight and that mild forms of diabetes may be cured by weight reduction. A few have suggested that decreasing the weight may have some small bearing on blood pressure levels. Finally there is some evidence that there is a greater amount of atherosclerosis percentage wise in people who are overweight as compared to those who are thin. But once again there are a lot of questions. For example we have no convincing proof that weight reduction will modify processes already present. In our own hypertensive clinic fat patients seem to live longer than thin ones. Much more study is needed.

Finally what of the role of fat in the diet? There does seem to be a relationship of some sort at least on a statistical basis between groups of people who eat a lot of fat and those who eat less. Disorders associated with high cholesterol levels in the blood seem to be those giving rise to hardening and scarring of arteries — atherosclerosis. Animals fed cholesterol will develop atherosclerosis in their blood vessels. And there are hundreds of statistical studies ranging from Bantus to Eskimos contrasting the incidence of atherosclerosis among different races, nations and even occupational groups. But what of proteins and carbohydrates? Some studies have shown that protein may not be innocuous in fact we speak of lipoprotein — fat molecules that hook up with protein molecules in our circulation. Other studies show that it is almost impossible to predict the individual's future on the basis of the cholesterol level, the size of fat molecule or anything else. In fact if one takes a diabetic or hypertensive population few differences can be seen in average values although the range of variety is somewhat greater in those with disease. And for every theory there is a counter theory. For example the Bantus appear to have less heart disease but they are often thin, may have liver disease and may have vitamin deficiencies. Perhaps other factors than diet are responsible. Eskimos rarely live to a ripe old age — one has to be careful

about making comparisons of groups of people unless they are contrasted from the standpoint of being the same age. One doctor in Great Britain showed that deaths from heart disease declined a little bit before fat rationing was introduced and then rose just after the fat rationing became more strict.

You are familiar with the line that one man's poison is another's meat. And so I would like to raise another problem. Mass statistics are very important. They give us clues. Ultimately it is the individual that should concern us. If there is more heart disease in the United States, does it mean that an entire population is more prone or that a few of us are more susceptible? This is another unanswered question but one which may be very important. Someday we would like to know how to distinguish the susceptible one so that he can be treated instead of an entire population. Furthermore, psychological disturbances increase when we impose restrictions on entire populations.

A year or two ago there was a meeting about the epidemiology of heart disease and hypertension. The conclusion was reached that there is more hardening of the arteries in men than in women, that there is more in older folk than in younger ones, and that there is an association of some sort between fat in the diet and the prevalence of coronary artery disease. All other reported associations remain hypothetical.

Until more knowledge is available, we can only try to approach a balance. The American diet is rather high in fat. It makes good sense to lower its fat content by hying away from butter and cheese and the fat on the margins of roast beef.

It seems to me we must retain a clear distinction between what we know and what is still a continuing experiment. This is not a plea for discarding any of the gains we have made or for throwing in the sponge; it is more a plea for retaining certain attitudes so that we can advance at a faster pace. What we really need to do is to devise and carry out more definitive studies to find continued support for the right kind of investigation. We are still at the beginning, and much needs to be done to elucidate the various pathways to a man's heart.

THE USEFULNESS OF DRUGS IN THE TREATMENT OF HYPERTENSION

HARRIET P. DUSTAN, M.D.

*Research Division, Cleveland Clinic Foundation, and the Frank
F. Bunts Educational Institute, Cleveland, Ohio*

The treatment of any disease aims to cure or failing this, to relieve its symptoms and prevent its complications. If the disease is one which runs a rapid and predictable course, such as an acute infection, the result of treatment can be evaluated in short order; in contrast, it may take years of patient effort to assess the effectiveness of a given treatment of a chronic

illness such as essential hypertension with its relatively unpredictable course. In those hypertensive patients whose treatment is aimed at the prevention of symptoms and complications that have not developed the results of preventive treatment can only be appreciated in general terms. Such preventive treatment is commonly used because most physicians believe that a significant degree of sustained hypertension will eventually have sequelae in the form of strokes or heart attacks which are caused in part at least by the blood pressure.

Hence while potent antihypertensive drugs have been widely used for the past seven or eight years the course of essential hypertension is so variable and usually so prolonged that many more years must pass before we can know whether these drugs are really as effective as they seem to be now. Still at the present time we can assess with confidence the effectiveness of these agents if we limit the consideration to that group of patients who suffer from a rapidly advancing form of the disease so called malignant or accelerated hypertension. This disease has a relatively brief and predictable course. Untreated it is rapidly fatal for nearly all such patients. For example in 1939 Keith Wagener and Barker summarized the clinical courses of 146 patients with malignant hypertension more than fifty percent of the were dead within six months some eighty percent had died by the end of the first year only two percent were alive at the end of the fourth year. At that time less than twenty years ago no really effective treatment was available thus a comparison of their survival with that of patients with malignant hypertension treated by modern methods can serve as an index of what has been our recent accomplishment.

The aim of treatment in hypertension is with due care to lower and maintain diastolic blood pressure at normal or nearly normal levels thus abating the symptoms and complications of the small blood vessel (arteriolar) disease characteristic of hypertension and preventing the complications of large blood vessel disease (arteriosclerosis) which is almost always accelerated by hypertension.

When we compared our group of sixty one malignant hypertensive patients whom we had treated during a five year period with that group reported about twenty years ago by Keith Wagener and Barker we found thirty percent of our patients died during the first year of treatment as opposed to eighty percent of theirs. It is important to realize that this thirty percent includes those patients who died in 1932 when we had little skill in the use of these antihypertensive drugs and little variety in their selection as well as those who died in 1950 when we had considerably more experience and a wider selection of drugs. Hence our experience in 1932 was understandably less gratifying than our more recent results. At the end of five years some thirty percent of our group was still alive while the comparable datum for the untreated group was two percent.

Thus modern treatment is definitely helpful in malignant hypertension this becomes more obvious when one examines the causes of death in the twenty eight patients who died during treatment. Ten advanced cases died of kidney failure and even of a peculiar pneumonia that complicated one kind of treatment. Five patients died of myocardial infarction four of cerebral hemorrhage and one of a ruptured aortic aneurysm. The cause of death of one patient is unknown. None of the patients died of heart failure which was previously an important cause of death. Of those who died of kidney failure all had extensive kidney disease before treatment was started. In short treatment has so changed the course of this type of hypertensive disease that patients no longer die of the effects of small blood vessel disease from the effects they usually recover. Some do so only to die months or years later of the complications of large blood vessel disease — arteriosclerosis.

There is no one drug for the treatment of malignant hypertension. Any of the antihypertensive drugs may be useful as long as the diastolic blood pressure is well controlled. This is the important point: diastolic blood pressure must be maintained at normal levels or as near normal levels as possible if the disease is to be well treated. The choice of a drug should be made according to the severity of the hypertensive disease and the response of the patient. If the patient is very ill and requires rapid blood pressure control a ganglion blocking agent is usually chosen. If a few more days or weeks of hypertension will not be harmful to the patient hydralazine or reserpine may be tried for although the effects may not be so promptly effective they are not so difficult to administer. In each instance the goal is the reduction of diastolic blood pressure to normal levels; not often is this goal achieved but we always strive for it.

Even though modern treatment of hypertension is effective many problems remain. We know so little about the fundamental mechanisms of the disease that our treatments are non specific furthermore they are clumsy for the patient and are often associated with troublesome and sometimes dangerous side effects. Because we do not understand the basic mechanisms we cannot predict the type of treatment which will be effective for a particular patient. Perhaps each of the drugs will lower his blood pressure perhaps none will or perhaps a combination of drugs will be the most helpful. Lately although we have accomplished a good deal in the treatment of severe and progressive hypertensive disease we are faced with the problem of the arteriosclerosis which has been accelerated by the pre existing hypertension. We are just beginning to face up to this problem seeking means for its prevention or cure. We hope that it will fade in importance as treatment becomes more specific prompt and lasting as a result of learning what are the basic mechanisms of the disease in all its various forms.

